AND GYNECOLOGY

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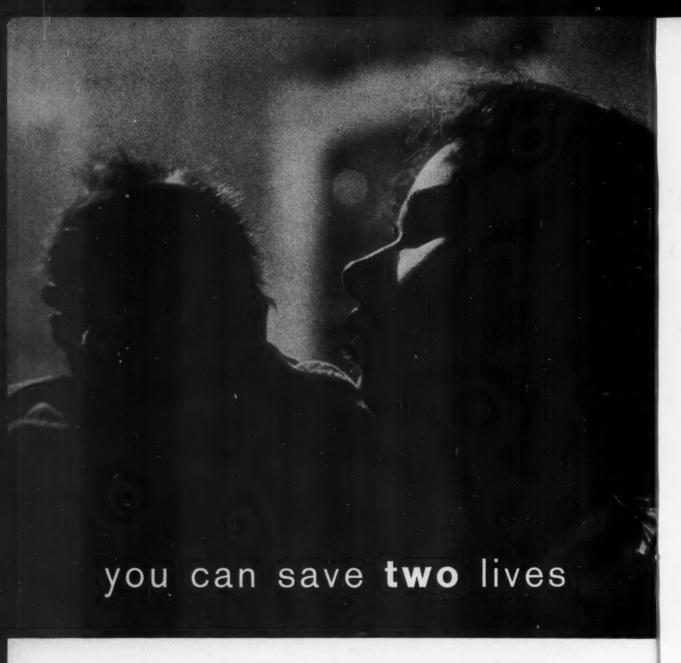
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AMERICAN GYNECOLOGICAL SOCIETY

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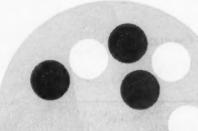
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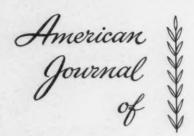
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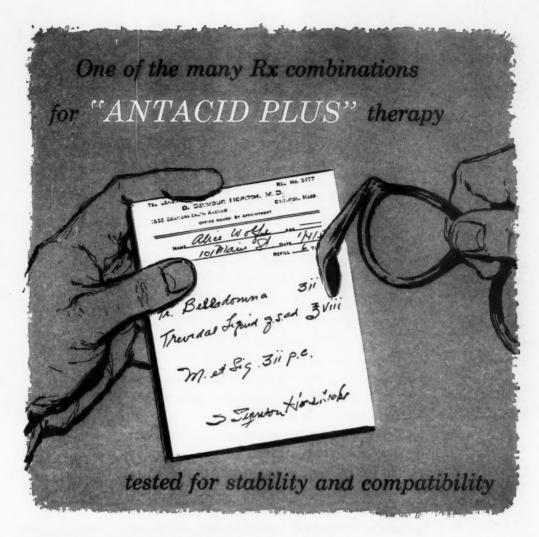
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Vol. 74, No. 2, August, 1957. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription rates: UnitedStates and its Possessions \$15.00, Students \$7.50; Canada, Latin-America, and Spain \$16.00, Students \$8.50; Other Countries \$17.50, Students \$10.00. Single copies \$2.50 postpaid. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A. Copyright © 1957 by The C. V. Mosby Company.



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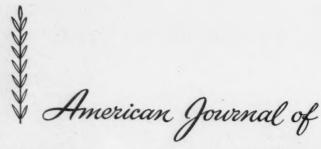
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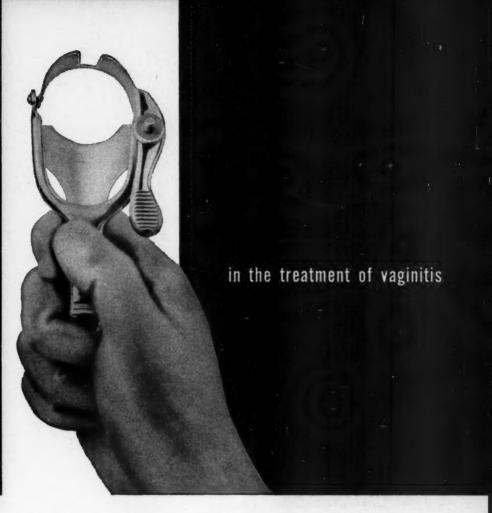
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Published by The C. V. Mosby Company 3207 Washington Blvd., St. Louis 3, Mo.

Entered at the Post Office at St. Louis, Mo., as Second-Class Matter.

Published Monthly. Subscriptions may begin at any time.

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Original Contributions.—Contributions, letters, and all other communications relating to the editorial management of the Journal should be sent to Dr. Howard C. Taylor, Jr., 622 West 188th St., New York 32, N. Y., or to Dr. William J. Dieckmann, 5841 Maryland Ave., Chicago

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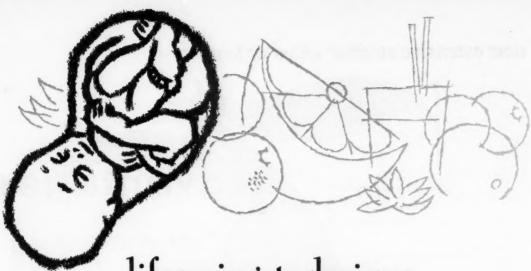
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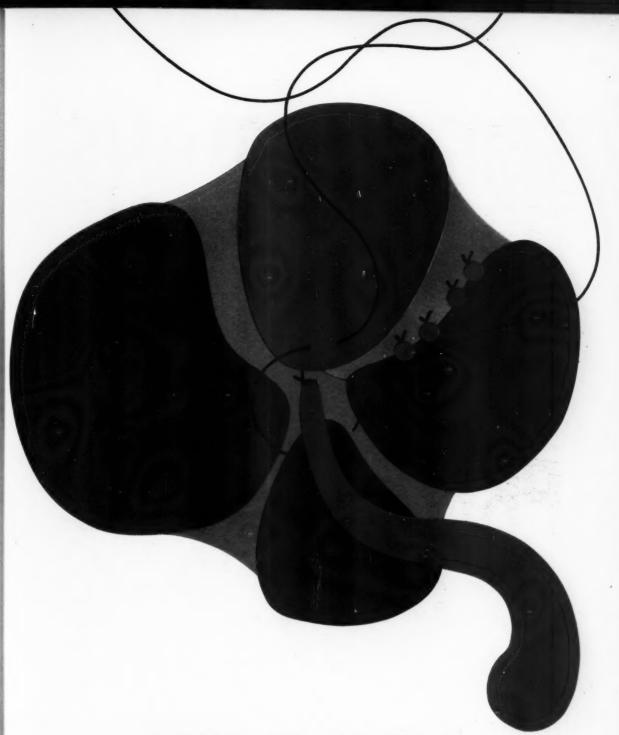
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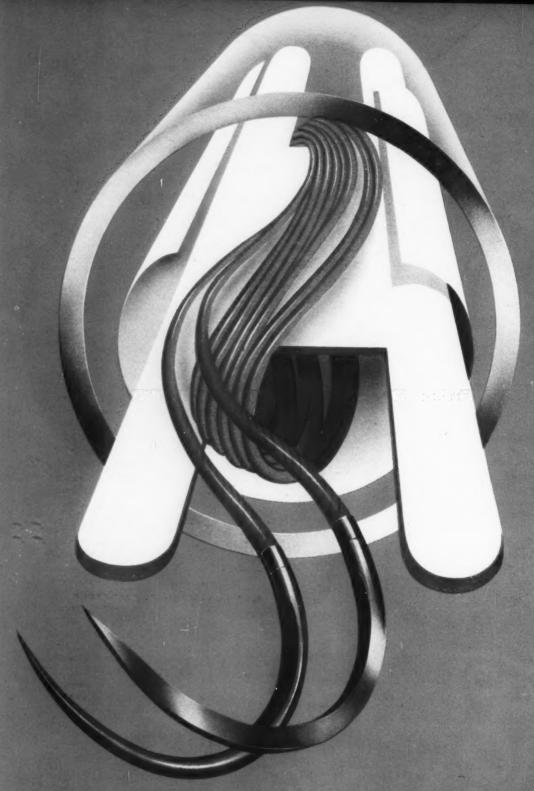
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IMFERON,® the new intramuscular iron-dextran complex, was introduced to American hematologists at the Sixth International Congress of the International Society of Hematology held in Boston, August 27 to September 1, 1956. Recent experience from over 6 million injections has shown that this iron preparation is easy to administer, notably free from toxic effects, quickly absorbed and productive of rapid hematologic and clinical improvement. It has been termed "...the only therapeutically effective iron preparation for intramuscular use..."

IMFERON meets the need for a safe, effective agent when parenteral iron is preferable for patients with iron deficiency anemia who are resistant or intolerant to oral iron, those with depleted iron reserves and those who require rapid restoration of hemoglobin, e.g. last trimester of pregnancy.

Previous parenteral iron preparations were unsatisfactory because of toxicity, pain on injection, or because they contained insufficient iron. IMFERON contains the equivalent of 5 per cent elemental iron. It is more stable than iron saccharate both *in vitro* and *in vivo* and does not precipitate in plasma over a wide pH range. It is isotonic with tissue fluids and has a pH of 5.2 to 6.0¹ Utilization for hemoglobin formation is almost quantitative.

Precision Therapy with IMFERON: Before treating a patient with IMFERON, total iron requirement is calculated by formula or determined from a convenient dosage chart. Then appropriate amounts of IMFERON are injected daily or every other day, until the total calculated required amount is given.

Iron Deficiency Anemia of Infancy: IMFERON provides a convenient safe means for restoring hemoglobin levels and iron reserves in anemic infants. Excellent results were obtained by Gaisford and Jennison² with IMFERON in 100 iron-deficient infants. From a pretreatment average of 54.5 per cent, hemoglobin levels rose to 87 per cent 10 weeks after the start of therapy.

References: (1) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: Progress in Hematology, New York, Grune & Stratton, Inc., 1956, vol. I, p. 25. (2) Gaisford, W., and Jennison, R. F.: Brit. M. J. 2:700 (Sept. 17) 1955. (3) Wallerstein, R. O.: J. Pediat. 49:173, 1956. (4) Sturgeon, P.: Pediatrics 18:267, 1956. (5) Jennison, R. F., and Ellis, H. R.: Lancet 2:1245 (Dec. 18) 1954. (6) Scott, J. M., and Govan, A. D. T.: Brit. M. J. 2:1257 (Nov. 27) 1954. (7) Grunberg, A.,

Clinical improvement paralleled this response. Premature infants and surgical cases were similarly benefited. IMFERON gave "...all the advantages of transfusion or intravenous therapy without the disadvantages." There were no side effects in any of the infants treated. Wallerstein confirmed these results, furnishing evidence that IMFERON is well absorbed and appears in the bone marrow 12 to 24 hours after injection. Results are equal to those with intravenous saccharated iron oxide without the unpleasant side effects. Sturgeon showed that the first year's iron requirements in infancy can be supplied with three injections of IMFERON. Iron Deficiency Anemia of Pregnancy: Nausea precludes oral iron therapy in many anemic pregnant women. In those with severe anemia who

cludes oral iron therapy in many anemic pregnant women. In those with severe anemia who are first seen late in pregnancy, prompt hemoglobin regeneration is unobtainable with oral iron. IMFERON produced prompt hemoglobin responses in anemia of pregnancy, ^{5,6} the results being similar to those obtained with intravenous saccharated iron oxide. Side effects were virtually absent with IMFERON. ^{5,6}

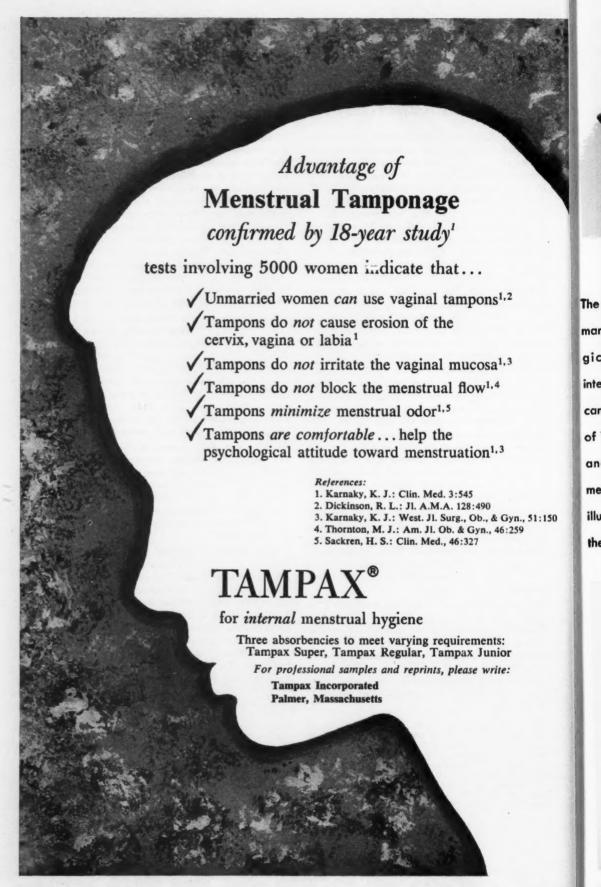
Resistant Hypochromic Anemia: Patients who do not respond to oral iron, those who cannot take oral iron and those with gastrointestinal pathology respond well to injections of IMFERON.⁷⁻¹¹ While oral iron is of little value in treating the anemia of rheumatoid arthritis, IMFERON is "...as beneficial as intravenous iron and easier to administer."

Present Studies: Published reports and recent findings of clinical investigators confirm the effectiveness and safety of IMFERON for hemoglobin regeneration and creation of iron stores. More than 70 studies are now being completed in the United States. Reports stress prompt hemoglobin response, ease of administration and freedom from side effects. Clinicians desiring additional information should request Brochure No. NDA 17, IMFERON, Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin.

and Blair, J. L.: A.M.A. Arch. Int. Med. 96:731, 1955. (8) Millard, J. B., and Barber, H. S.: Ann. Rheumat. Dis. 15:51, 1956. (9) Baird, I. M., and Podmore, D. A.: Lancet 2:942 (Nov. 6) 1954. (10) Cappell, D. F.; Hutchinson, H. E.; Hendry, E. B., and Conway, H.: Brit. M. J. 2:1255 (Nov. 27) 1954. (11) Stevens, A. R.: A.M.A. Arch. Int. Med. 96:550 1956.

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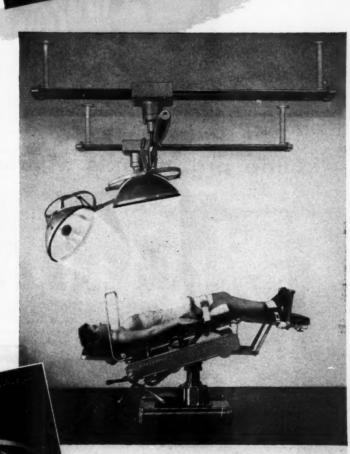
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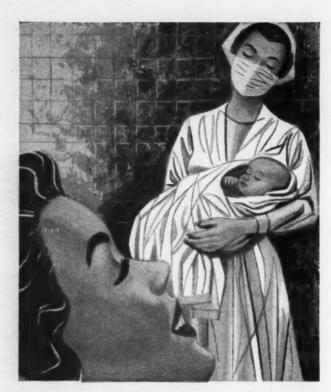
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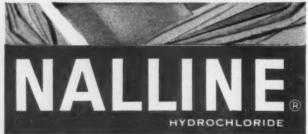
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REFERENCES: 1. Rives, H. F.: Texas J. M. **52**:224, 1956.
2. Diggs, E. S.; Prevost, E. C., and Valderas, J. G.: Am. J. Obst. **71**:399, 1956. 3. MacLeod, P. F., et al.: Internat. Rec. Med. **169**:561, 1956.

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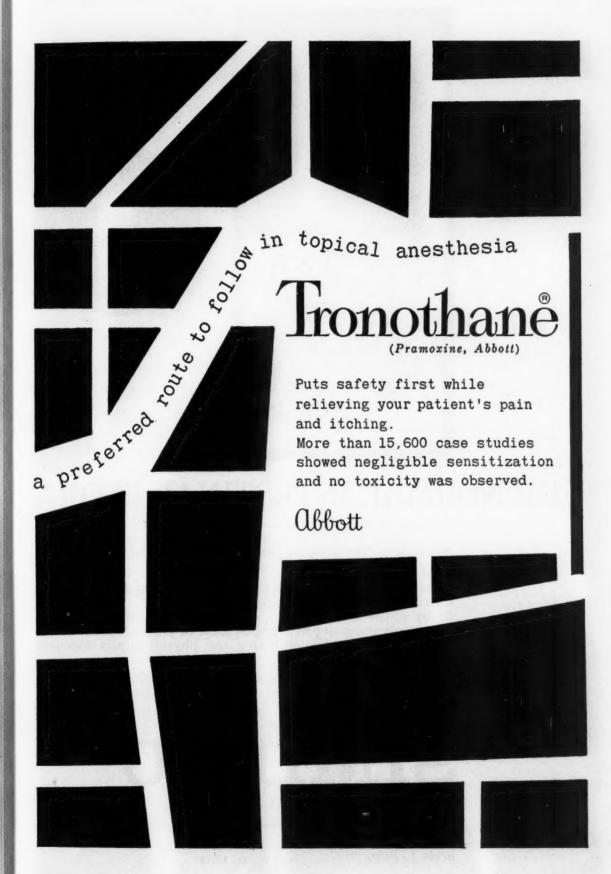
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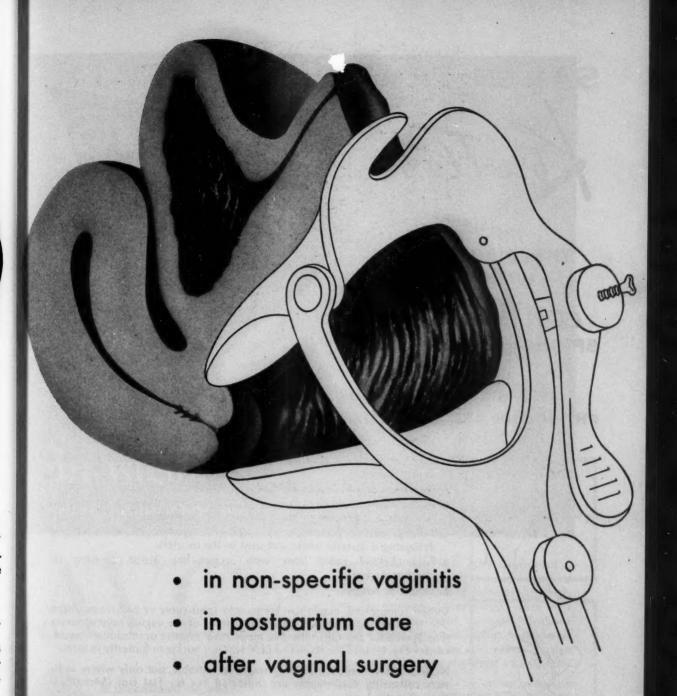
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FIG. 1





FIG. 2



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- 2. Conserves physician's time by reducing fitting and instruction period.
- 3. Patients learn readily and develop greater confidence because of the ease with which they learn to place and use the diaphragm.
- 4. Affords patient protection by locking in spermicidal lubricant and delivering it directly under and next to the os uteri.
- 5. Folds behind pubic bone with suction-like action forming an effective barrier.
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When compressed, diaphragm forms into semi-curve or half-moon shape (Fig. 1) permitting it to pass easily along floor of the vagina beyond cervix (Fig. 2) without any difficulty. No mechanical inserter or introducer required (see Fig. 2) since the KORO-FLEX will not buckle or butterfly in form.

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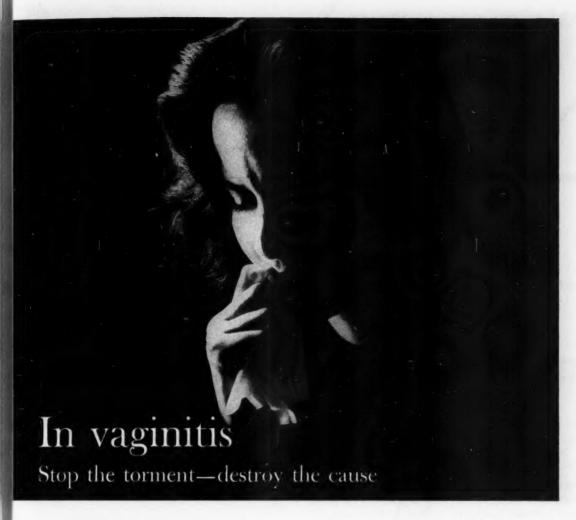
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Composition: A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

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Administration: An applicatorful twice daily—on arising and at bedtime.

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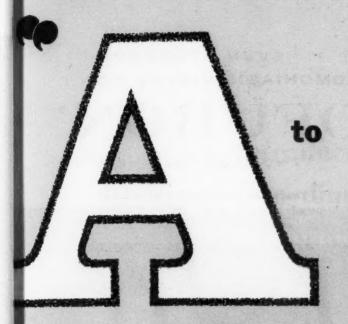
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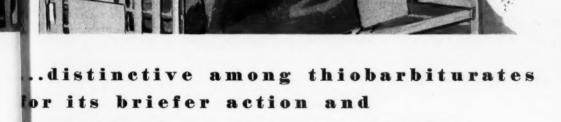
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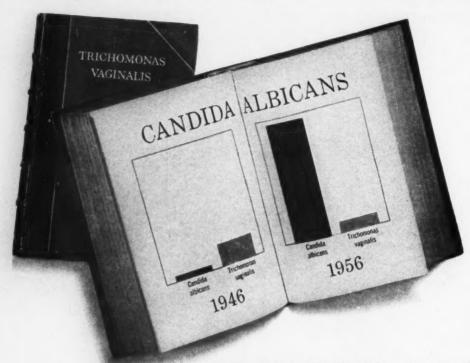
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References: 1. Dinkel, R. M.: Eugenics Quart. 3:22 (Mar.) 1956. 2. Grove, R. D.: Am. J. Pub. Health 46:592 (May) 1956. 3. College Study Report: Population Bulletin 11:45 (June) 1955. 4. Novak, E., and Novak, E. R.: Textbook of Gynecology, Baltimore, The Williams & Wilkins Company, 1956. 5. Tietze, C.: Proc. 3rd Internat. Conf. Planned Parenthood, 1953.

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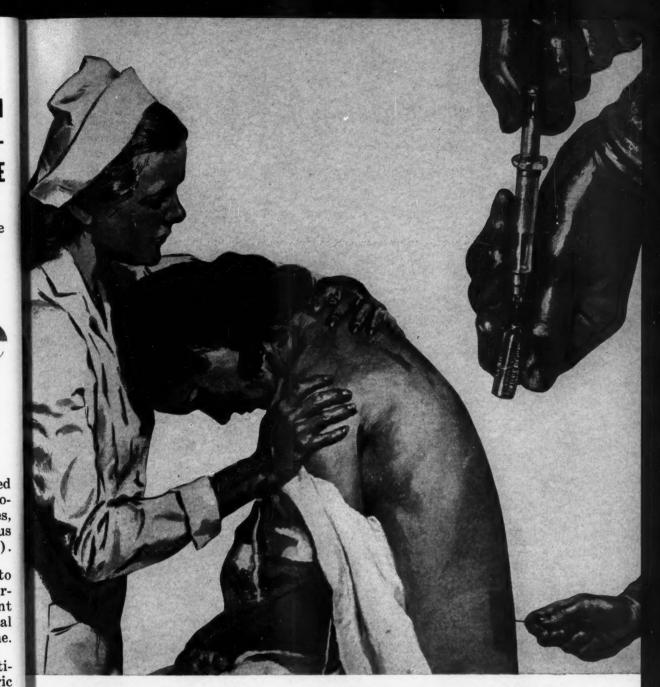
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1. Doyle, J. C.: Urol. & Cutan. Rev. 55:618 (Oct.) 1951. • 2. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657. • 3. Doyle, J. C.: California Med. 71:15 (July) 1949.

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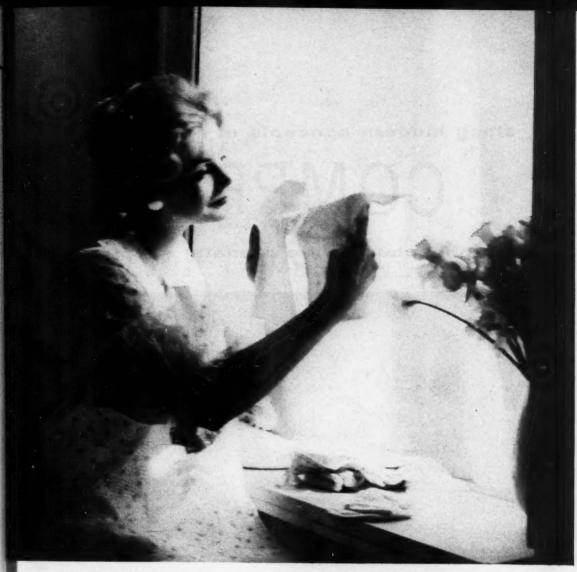
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OBSTETRICS AND GYNECOLOGY

Obstetrics

ROUTINE CURETTAGE AT DELIVERY*

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Gyn

THE purpose of this presentation is merely to record the procedure and results of curettage of the uterus at the time of delivery, not as an emergency measure but as a routine practice.

My¹ interest in the control of postpartum bleeding began in 1940. Although trained in the conservative as opposed to the radical² school of treatment of incomplete abortion, I later observed that more frequent curettage and emptying of the aborting uterus saved blood, lessened morbidity, and possibly often preserved fertility. With the observation that the postabortal course was shortened by removal of blood clots, placental debris, membranes, and decidua, the question arose as to why such a practice should not as well be applied at full-term delivery as at abortion.

In 1947, with a few papers³⁻⁸ cautiously appearing about manual palpation of the uterus following delivery, I initiated the maneuver of routinely invading the uterus. The availability of antibiotics, of course, lent reassurance where only a few years previously one would have been horrified to attempt such a transgression of obstetrical teaching. Actually, Holmstrom's⁹ paper on the bacterial flora of the uterus shows why invasion of the postpartum uterus immediately following delivery is not very likely to cause infection, for it is after the first 48 hours that pathogenic bacteria begin to appear. Entering the uterus with the hand, as in the more and more widely accepted practice of manual removal of the placenta, not only may not arouse bleeding but may very efficiently control it.

^{*}Condensed from a paper presented at a meeting of the North Carolina Obstetrical and Gynecological Society, April 29, 1956.

The danger of perforation of the uterus with a curette is a relative matter. With ordinary care, this accident will not happen unless there is mechanical difficulty in entering the uterus as in the presence of cervical stenosis or carcinoma.

Method

The curette* used is a large sharp instrument with a blade, the loop of which is 1 inch wide. The shaft is malleable to allow adaptation to the varying axes in which one finds the uterine canal. The blade is large, not to avoid perforation but to effect a more complete scraping of the interior of the uterus than would be possible with ordinary curettes. Since the uterine cavity is often flattened anteroposteriorly when contracted, it may not be possible to rotate such a large curette; in this case it is simply withdrawn and reinserted after rotation. The free hand is placed on the abdomen in contact with the top of the fundus. By this means the curette can be felt to impinge against the top of the fundus from within as it is inserted. This gives an accurate knowledge of its depth of penetration, which is quite different from the situation in curetting the smaller postabortal uterus. With this hand also, the axis of the fundus can be adjusted to the direction of the curette much as one would manipulate a carton to scrape out the contents with a spoon. The hand is more sensitive to the feeling of the curette against the wall of the fundus than one might suppose: the feeling of the presence of membranes gives a slippery, mushy sensation; placental tissue is more doughy; and clean uterine wall gives the sandy scraping usually noted in curettage of the nongravid uterus.

Results

The accompanying tables will be seen to be more or less self-explanatory. There are some features of each, however, that will be worthy of comment.

TABLE I. MORBIDITY

	NO.	CASES	%
Total for study		715	
Nonmorbid.—			
Temperature:			
Normal		514	72
100-101° F. once only 12-18 hours post partum	95		
100-101° F. once only 24-72 hours post partum	46		
Single temperature elevation		141	20
Total		655	92
Morbid.—			
Undetermined cause	12		1.6
Cystitis	18		1.0
Ante/intrapartum sepsis	11		
Postpartum sepsis (foul lochia)			
Enteritis	2		
Mastitis	3 2 4 2 1		
Packing	2		
Aspiration bronchitis	ĩ		
Infectious mononucleosis	1		
Abscess of Bartholin gland			
Respiratory infection	1 2		
Hematoma	3		
Hematoma			
Total		60	8.4

^{*}Made to order by the J. Sklar Manufacturing Co.

The total number of records reviewed for this study has been 715, from which the percentage figures are derived.

The single elevations of temperature noted in Table I are of interest. The temperature, normal on admission, usually is not again checked until following delivery and often not until the patient has been returned to her room. The elevations, at least through 18 hours post partum, are conceivably due to dehydration. Those which rose 24 to 72 hours post partum are probably due to a transient bacteremia; but this is not necessarily in any way related to the process of curettage, for the same elevations are frequently found in patients who have not been curetted.

The morbidity statistics are a little more critical than the customary standard of temperatures of 100.4° F., for I have used a level of 100.0° or over for 2 successive days excluding the day of delivery. There was no mortality.

It is noteworthy that curettage was done in those patients with antepartum and intrapartum sepsis as well as one with an acute abscess of the Bartholin gland without apparent complication of the course of recovery. Perhaps this is again due to the antibiotic drugs.

The 12 patients (1.6 per cent) who exhibited morbidity without any explainable reason were the only ones in whom curettage might have been a factor in producing morbidity. This was not apparent, however, for there was no evidence of foul lochia, tender uterus, or pelvic phlebitis for which such a procedure might be condemned.

In Table II is shown the number of patients in whom antibiotics were used and the reasons therefor. The 34 patients given penicillin prophylactically were those early in the course of the study at which time I was not certain of the safety of the procedure. It also includes those in whom possible contamination was feared. Nonetheless, only 9.9 per cent were given penicillin primarily because of the curettage.

TABLE II. ANTIBIOTICS

	NO.	CASES	%
Total for study		715	
No antibiotic		530	74
Antibiotics given for expected morbid states Antibiotics given for present morbid states	64 50		
Total unrelated to curettage		114	16
Antibiotics used: Prophylactically For unexplained fever For foul lochia (nonmorbid)	34 34 3		
Total possibly related to curettage		71	9.9

TABLE III. RESULTS OF CURETTAGE

	NO. CASES	%
Total for study	715	-
No unusual feature mentioned on record	654	91
Fragment of membranes removed Fragment of placenta removed	47 9	
Total effective prevention of hemorrhage	56	7.8
Additional comments:		
Hemorrhaged until curetted Marked amount of decidua	1 4	

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In Table III the 7.8 per cent of patients in whom curettage removed tissue is to be compared with the 6 per cent incidence of retained placental tissue reported by Weekes and O'Toole¹⁰ as a cause of postpartum hemorrhage. Shulman and associates¹¹ reported 9 per cent of delayed postpartum hemorrhages to be due to retained secundines.

It is a comforting feeling to remove pieces of placenta or membranes after inspection of the placenta and membranes has in many cases shown no deficiency grossly. In one patient, so much membrane was removed by the curette that further inspection of the placenta showed this must have been the entire chorion. This comment is found on the delivery note of another patient who had had hydrorrhea since the fifth month: "Curettage removed quite a quantity of fragments of necrotic membranes; placenta apparently normal."

On several occasions it was noted that "curettage removed a large amount of decidua." One patient was found on manual removal of the placenta to have an incomplete septum of the uterus. The placenta was found in one cornu, while an unusually abundant quantity of decidua was curetted from the opposite cornu. Of what significance this disproportionate amount of decidua may be is pure conjecture. All these patients had normal postpartum lochia. I suspect it might have been abnormally heavy or prolonged had curettage not been done.

For several reasons tissue was not prepared routinely for microscopic examination. A number of sections, unselected, were made of samples of curettings and examination of the slides shows the following common features: (1) sheets and strips of decidua in all cases; (2) within the decidua, numerous flattened, thin-walled, endothelium-lined sinusoids, most of which were empty; (3) no or very slight evidence of inflammatory infiltration of round cells, except in those patients who had had previous rupture of the membranes or a morbid intrapartum course; (4) scant evidence of placental villi; (5) occasional strips of myometrium, but less than one might presuppose; (6) small, thick-walled vessels with occasional fresh thrombus formation.

In evaluation of Table IV, it should be realized that the great majority of these patients were delivered under low spinal anesthesia with which the

TABLE IV. BLOOD LOSS AT DELIVERY

	NO. C	ASES	%
Total deliveries		715	
Bleeding not described	31		
Total for study		684	
Minimal or scanty* bleeding	63		
Normal bleeding	584		
Total normal blood loss		647	95
Moderately heavy bleeding:			
Uterine, from ether anesthesia	5		
Extrauterine (lacerations, varices, etc.)	27		
Total moderately heavy blood loss		32	
Excessive blood loss:			
Uterine	2 3		
Lacerations	3		
Total excessive blood loss		5	0.7

^{*}Bleeding so slight as just to stain the perineal drape.

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of the blood loss at delivery is considerably less than with the use of general anesthesia, especially ether. Only 0.7 per cent had an exaggerated loss of blood and this was unrelated to curettage.

In Table V there was one instance of postpartum hemorrhage truly from retained secundines. Curettage was repeated about 2 hours after delivery and a strip of membrane removed described as 1 by 4 inches in size. This episode showed that thorough and careful curettage is important. The curette must "feel" a clean uterus, that is, produce the sandy scraping previously noted.

TABLE V. LOCHIA DURING HOSPITAL PERIOD

	NO.	CASES	%
Total for study		715	
Scant	14		
Normal	694		
Total with lochia within normal limits		708	99.1
Postpartum hemorrhage:			
Thrombocytopenic purpura	1		
Retained secundines	1		
Ambulation on day of delivery	1		
Subinvolution sixth day	1		
Hematoma	2		
"More than normal," transfused	1		
Total with excessive lochia		7	0.9

TABLE VI. LOCHIA AFTER DISCHARGE FROM HOSPITAL

	NO.	CASES	%
Total deliveries		715	
No follow-up	40		
Total for study		675	
No comment (assumes lochia less than 3 weeks)	618		
Lochia 3 days to 3 weeks	18		
Total with lochia less than 3 weeks		636	94
Lochia lasting 4 weeks	10		
Lochia lasting 5 weeks	1		
Lochia lasting 6 weeks	21		
Total with moderately abnormal lochia		32	4.3
Late hemorrhage, "retained secundines" (no slide)	1*		
Late hemorrhage, thrombocytopenic purpura	1		
Late hemorrhage, subinvolution sixth day	2*		
Late hemorrhage, subinvolution ninth day Late hemorhage, endometritis	1*		
(12-15 days post partum)	2*		
Total with postpartum hemorrhage		7	1.0

*See discussion in text.

The two cases of extraordinarily scant lochia seen in Table VI are of particular interest. They represent the same patient, her delivery in 1949 followed by no lochia whatever until the seventh day. I have never encountered this before and was daily expecting severe hemorrhage to occur. In her postpartum course in 1952 she had very scanty lochia for only 3 days,

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TABLE VII. RETURN OF MENSTRUATION

	NO.	CASES	%
Total deliveries		715	
No follow-up	151		
Total adequately followed for study		564	
Onset of menstruation:			
4 weeks	19		
6 weeks to 3 months	306		
Total menstruating by 3 months		325	58
3 to 8 months	142		
No period before next pregnancy	3		
Specific onset unknown; regular by later history	83		
Total menstruating by 8 months		224	39
Grand total with onset of menstruation within			
normal range		549	97
Amenorrhea to last contact at 6 months	1		
Menses irregular 1 year or more	$\frac{1}{2}$		
Amenorrhea 21 months (Sheehan's syndrome)	1		
Subsequent bleeding problem, functional	11		
Total subsequent menstrual abnormality		15	2.

TABLE VIII. SUBSEQUENT FERTILITY

	NO.	CASES	%
Total deliveries		715	
Inadequate follow-up	180		
Total adequate follow-up for study		535	
Contraception	205		
Sterilized	38		
Widowed	3		
Later hysterectomy	3		
Total excluded from possible fertility		249	
Corrected total for study		286	
Delivered 1 year later	41		
Delivered 2 years later	95		
Delivered 3 years later	65		
Delivered 4 years later	21		
Delivered 5 years later	18		
Delivered 6 years later	6		
Delivered 7 years later	2		
Delivered 8 years later	2		
Total normal next pregnancies		250	88
Patients having 2 more babies, also curetted	40		
Aborted subsequent pregnancy	19		
Therapeutic abortion, subsequent pregnancy	3		
Criminal abortion, subsequent pregnancy	3		
Placenta previa, subsequent pregnancy	1*		
Abruptio placentae, subsequent pregnancy	1*		
Ruptured ectopic pregnancy 1 year later	1		
Congenital abnormality, subsequent pregnancy	2		
Sterility problem later (of these, husband 1, endometriosis 1)	6		
Total unsatisfactory later history		36	12

^{*}Normal babies obtained.

following which there was nothing more than a normal leukorrhea. I have seen this occur in one other patient curetted since then who is not included in this study.

"Retained secundines" was a presumptive diagnosis on the hospital records without tissue proof in 2 cases in which the lochia continued to six weeks and one which was so designated at the seventh day. In the light of studies of the tissue obtained in those with "late hemorrhage," the diagnosis of "retained secundines" was probably incorrect. Six of the cases designated as "late hemorrhage" were originally diagnosed on the hospital records as "retained secundines." A review of the slides made from the curettings at the time of their hemorrhages, however, proves otherwise. In one of these the slide has been lost and, remembering the character of the patient, I am inclined to think that her hemorrhage was due to subinvolution from activity rather than to "retained secundines" as shown in the table. Examination of the slides in the remainder of these 6 cases shows no chorionic villi. The slides show myometrium with endometrial glands, fresh hemorrhage, and infiltration of inflammatory cells. Thus, there was no case of late hemorrhage due to retained secundines.

Of the 2 cases of late hemorrhage 12 to 15 days post partum, one patient had previously had a partial placenta accreta followed by 21 months of amenor-This time again she had a partial placenta acccreta requiring manual removal of the placenta.

Table VII, showing a 97 per cent normal return to menstruation, seems sufficient evidence to refute the preposterous statements found in the literature regarding the effect of curettage, two of which are quoted:

Dr. J. Mathieu¹² of Lyon observes that "amenorrhea is seen more frequently when dilatation and curettage is done post partum than when done after abor-Extensive scarring and formation of intrauterine adhesions obliterate the cavity. Hysterographic examination usually reveals deformity of the cavum uteri, with or without visible adhesions.'

"In an otherwise excellent discussion of postpartum amenorrhea, your consultant seems to have neglected to mention the most probable etiological factor in this case, namely, curettage. This procedure, particularly when done in the early postpartum period, is certainly not a rare causative factor in prolonged or permanent amenorrhea."13

The lack of harmful effect on subsequent fertility is shown in Table VIII. A normal outcome of 88 per cent of further pregnancies is well above the accepted figure of 20 per cent pregnancy wastage so often quoted. 14-16

Conclusions

A study of the routine curettage of the uterus immediately post partum in 715 patients has been presented. The evidence tends to show that it is not a dangerous procedure. The morbidity rate may be moderately improved, blood loss at delivery is reduced, and 7.8 per cent of patients were found to have retained tissue at delivery which might have caused later hemorrhage. Postpartum lochia is both lessened and shortened, and subsequent menstruation and fertility are not adversely affected.

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CERVICAL INCOMPETENCE: REPAIR DURING PREGNANCY

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WHAT can be done for the pregnant patient with a history of one or more late abortions or premature labors secondary to spontaneous premature rupture of the membranes? Many times the true diagnosis, usually cervical incompetence, was neither suspected nor verified following the previous fetal loss. Even suspected cases of cervical incompetence may not be proved unless the gradually dilating cervix is demonstrated by repeated vaginal examinations, a procedure done too infrequently in these cases. A survey of the standard textbooks and related literature fails to disclose information of value in the diagnosis or therapy of such patients during pregnancy prior to rupture of the membranes, other than the recommendation of bed rest throughout the gestation.

There are some articles available dealing with the diagnosis and therapy of the incompetent internal os in the nonpregnant state. Lash and Lash⁵ in 1950 reported on the incompetent internal os as a cause of habitual abortion, usually during the second trimester. They stated that "the degree of incompetency may vary so that habitual abortion may not always occur if the defect is slight, especially if the patient is restricted to the supine position for months until term is approached in order to prevent the herniation of the dependent bag of waters or presenting part through the partially open internal os." They also listed many factors as the cause of this condition, including overdilatation of the os, overzealous curettage, previous abortion followed by dilatation and curettage, vaginal hysterotomy or cesarean section, abdominal lower segment cesarean section, rapid labor, traumatic forceps delivery, and extraction of the shoulders through an unrecognized constriction ring. Palmer⁶ additionally emphasized congenital and neuromuscular factors. Danforth, in his discussion of the Lashes' paper, expressed the opinion that the entire cervix was involved, not just the internal os, since abortion frequently occurred during pregnancy following high amputation of the cervix. Fisher² substantiated Danforth's statement when he found that high amputation of the cervix caused a subsequently increased incidence of premature delivery and late abortions. He also recommended the Sturmdorf procedure as a safer alternative to cervical amputations in young women. Rubovits and associates7 in 1953 published methods of radiographic diagnosis of the incompetent internal os of the cervix and gave further techniques for surgical repair in the nonpregnant state. It should be re-emphasized that these papers all referred to the diagnosis and treatment of this condition in the nonpregnant patient, not in patients already pregnant and prior to spontaneous rupture of the membranes.

It was not until the meeting of the United States Branch of the International Fertility Association in December of 1955 that the first valid suggestion concerning worth-while therapy during pregnancy was brought to our attention. Greenhill³ stated that he knew of one case where the cervix had been sutured shut, after conception had occurred, with later delivery of a living infant. Then Hall4 reported his case of cervical incompetence following high amputation of the cervix, which he treated by encircling the uterine opening with nylon filament at 5 to 6 weeks' gestation. When the membranes ruptured spontaneously at 34 weeks' gestation, this suture was simply cut, allowing an uneventful delivery of a living infant. Greenhill's valuable bit of information influenced us to do something constructive toward obtaining living babies for these women. The practicality of such a procedure and the type of procedure to be done, however, remained to be determined in a case where definite cervical incompetence of surgical degree was found during pregnancy and prior to the rupture of the membranes. The procedure is not new, nor even difficult, but it is the first reported trachelorrhaphy done during pregnancy and with intact membranes, to the best of our knowledge.

Case Report

History.—Mrs. E. C., a 37-year-old gravida v, para ii, with 2 abortions, an infertility patient, was admitted to the hospital on May 3, 1956, with a pregnancy of 25 weeks' duration. The estimated date of confinement was Aug. 16, 1956. She was admitted directly from the senior author's office, where routine pelvic examination had shown cervical dilatation of 2 to 3 cm., 25 per cent effacement, and intact membranes bulging down to within 1.5 cm. of the external os. The patient was relatively asymptomatic and no uterine contractions were noted.

The previous obstetrical history disclosed that in 1943 her first pregnancy was terminated at 37 weeks by premature spontaneous rupture of the membranes and spontaneous delivery of an 8 pound infant. In 1946, the second pregnancy resulted in spontaneous delivery of an 8 pound, 12 ounce infant at term. A curettage was done in 1954 for spontaneous incomplete abortion at 10 weeks' gestation without premature rupture of the membranes. In April of 1955 she had an abortion two hours after spontaneous rupture of the membranes at 12 weeks' gestation. At the curettage at this time a uterine septum dividing the fundal area into right and left portions and extending about 2 cm. into the uterine cavity was suspected.

Following this miscarriage, the patient was started on routine "sterility" studies. Laboratory examination showed only a low hemoglobin of 10.5 Gm., and a basal metabolic rate of minus 12. The patient, her husband, and both sons all had type O, Rh-negative blood. Ovarian function seemed satisfactory since endometrial biopsy (late secretory), basal body temperature, comparative palm-leaf tests, and Spinnbarkeit tests all gave evidence of ovulation. Carbon dioxide readily passed through the Fallopian tubes at 40 to 60 mm. of Hg. X-ray studies of the endometrial cavity showed a slightly arcuate uterus with no definite septal defect but some evidence of mild incompetency of the internal os. The tubes appeared normal and patent to the dye. Pelvic examination disclosed a rather severely lacerated, grossly incompetent external os. However, no larger dilator than a No. 4 Hegar could be passed through the internal os without discomfort.

On Dec. 12, 1955, the patient returned with the present pregnancy, stating that the last menstrual period was Nov. 8, 1955. Routine laboratory examination showed: hemoglobin 12.0 Gm. per 100 ml.; the urine was normal; Kline test negative; indirect Coombs test negative; Rh titer negative. On Jan. 14, 1956, she was placed on vitamin K (5 mg. daily) and Doriden (0.5 Gm. three times a day temporarily) for mild sedation because of slight spotting. Hospitalization was required later that same day because of increased bleeding.

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At this time the thyroid was increased to 1 grain daily and intramuscular aqueous progesterone, 25 mg. every 6 hours, was given, in addition to bed rest and the previous therapy. She was dismissed on Jan. 16, 1956, symptom free. Fetal movement was first felt on Feb. 22, 1956, at 15 weeks' gestation. Progress was then uneventful until the hospitalization for surgical closure of the incompetent cervix to prevent spontaneous rupture of the membranes and subsequent fetal loss from premature labor.

Surgical and Postoperative Course.—On admission May 3, 1956, for surgical therapy the patient was placed on strict bed rest and given Doriden, 0.5 Gm., for sedation. By the next morning the cervix was dilated to the size of a half dollar and the intact membranes bulged even more. She was taken to the operating room on May 5, 1956, and under intravenous anesthesia a trachelorrhaphy was done, with extreme care to avoid the membranes. A strip of mucosa 1 to 1.5 cm. wide was excised from the inner surface of the external os and in the form of a right and left "V," each "V" pointing laterally at 3 and 9 o'clock in the region of previous old bilateral cervical lacerations. Only a centrally located area of mucosa about 0.5 cm. length was left undisturbed. When interrupted sutures of No. 1 chromic catgut were placed anteroposteriorly about 1 cm. apart and then pulled snug, the anterior and posterior raw surfaces of the external os were approximated over the membranes, leaving a central opening about 0.5 cm. in diameter for drainage and later identification of the new external os. No drain was placed through this central opening for fear of erosion and rupture of the membranes. The pathologist reported the excised cervical tissue to be normal.

Postoperatively, the patient was put on strict bed rest, and was given Dilaudid, ½32 grain every 4 hours, and later Doriden, 0.5 Gm. every 6 hours. Over the next 12 days she also received 1,245 mg. of aqueous progesterone intramuscularly, with a peak of 200 mg. daily in divided doses. The first 66 hours of the postoperative course she was given 60,000 units of oral Lutrexin, some in doses of 4,000 to 6,000 units hourly. For the entire 12 days she received a total of 127,000 units of Lutrexin. Tetracycline, 250 mg., with Nystatin, 250,000 units, was given every 4 hours and no temperature elevation was encountered. The immediate postoperative course was marked by near labor on several occassions. On May 16, 1956, a vaginal examination revealed an intact cervical suture line and she was discharged on bed rest, Hesper-C (1 capsule three times a day), thyroid extract (1 grain daily), Lutrexin (1,000 units three times a day), vitamin K (5 mg. daily), and Natabec (1 capsule daily). The Lutrexin and vitamin K were discontinued after one week, while the other medication was maintained until hospitalization for delivery.

Delivery and Postpartum Course.—On July 11, 1956, at 35 weeks' gestation, the patient was admitted in spontaneous labor and with the membranes intact. Labor had begun at 2:45 A.M., and by 4:50 A.M. sterile vaginal examination showed 2 cm. cervical dilatation, a minus 1 station, left occipitoanterior position and the membranes still intact. The cervix was extremely thin in the region of the previous trachelorrhaphy. Labor and dilatation progressed normally, and after a total of 5 hours and 41 minutes of labor a 7 pound, 11 ounce live infant was delivered spontaneously. A more thorough cervical trachelorrhaphy was done immediately post partum. Chest x-ray was negative.

The postpartum course was uneventful. Examination at 8 weeks post partum revealed complete involution of the uterus. The cervix measured 1 inch in length and a No. 4 Hegar dilator traversed it with slight discomfort.

Comment

Cervical incompetence may be classed as complete or incomplete. Complete incompetence would involve the entire cervical structure, while incomplete incompetence would concern either the supravaginal portion or the vaginal portion of the cervix. The supravaginal portion would include the internal os and the upper body of the cervix. The vaginal portion would include the external os and the lower body of the cervix. The latter type of cervical incompetence is

much more frequent than the supravaginal type, and incomplete incompetence more common than the complete form. We estimate that cervical incompetence of surgical degree occurs once in approximately every 300 consecutive pregnant women examined.

In the case presented, a mildly arcuate uterus may have predisposed the patient to premature labor. The internal os was definitely only "borderline" in degree of competency prior to the beginning of pregnancy. In addition, the external os and vaginal portion of the cervical body were grossly severely lacerated, failing to give proper support to the internal os and supravaginal portion of the body of the cervix. Only frequent vaginal examinations brought the gradually dilating cervix into clinical consideration in time to correct the situation. Obviously, any pregnant patient with a history and pelvic findings suggestive of cervical incompetence must have weekly cervical examinations if this disorder is to be diagnosed and adequately treated prior to premature spontaneous rupture of the membranes. Any cervix dilated over 1.5 cm. prior to the twenty-eighth week of gestation should be considered incompetent and trachelorrhaphy considered.

Treatment consists of careful trachelorrhaphy. It appears wise to delay this procedure until after the third month in the usual case, since prior to this time abortion is frequently due to a faulty conceptus, while after this stage a normal fetus may be expected. After the twenty-eighth week of gestation little is to be gained by attempts either to diagnose or to treat this entity, since a viable infant is then as likely without treatment as with it. After trachelorrhaphy, should labor occur in the immediate postoperative course, one need only cut the sutures, allow delivery, and then repair the cervix thoroughly. If the pregnancy continues until spontaneous labor ensues nearer term, Dührssen's incisions might prove necessary, followed by adequate repair of the cervix immediately post partum. We have attempted to use cervical caps and plastic bands encircling the cervix with no success. Medical therapy is of dubious value. Bed rest is of the utmost importance, however, and should be maintained if at all possible until a definitely viable infant is assured.

It is of passing interest that this patient's internal os was dilated 4 or more em. for the last two months of her pregnancy without stimulating labor. Apparently, so long as membranes remain intact, cervical dilatation and pressure on the cervix alone will not cause the onset of true labor.

Summary

A surviving infant was obtained at the thirty-fifth week of gestation, after a trachelorrhaphy was done at the twenty-fifth week to prevent spontaneous rupture of the membranes through a cervix dilated to 3 cm. An abundance of adjunctive therapy was used in addition to this simple surgical procedure.

An estimated incidence of surgical cervical incompetence in a practice heavily laden with grandmultiparas is 1:300, where the latter figure represents consecutively observed pregnant patients regardless of eventual abortion or delivery of a viable infant.

Addendum .- Since the preparation of this paper for publication, Greenhill, in a letter dated Sept. 13, 1956, has called our attention to another method of attack on this same problem by Shirodkar of Bombay, India. Shirodkar's paper, entitled "A New Method of Operative Treatment for Habitual Abortions in the Second Trimester of Pregnancy," describes his procedure which includes suturing a strip of fascia lata around the cervix at the level of the internal os, followed by cesarean section as the usual method of delivery at term. He reports only 4 failures out of 26 cases and recommends the procedure even when previous amputation of the cervix has been done.

We wish to express our gratitude to Dr. J. P. Greenhill for his valuable contributions; to Miss Maxine Thieme, R.N., for her cheerful and tireless assistance; and to Mrs. Wayne F. Baden for her devoted and encouraging secretarial efforts.

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FRACTURE OF THE PELVIS IN PREGNANCY

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In THIS modern machine age, when annually thousands meet death or receive crippling bone injury on the highways, one must commend the progress made in the fields of obstetrics and orthopedics to combat these ever increasing tragedies. In a review of the literature, however, it was found that the attention given to traumatic rupture of the uterus far outweighs the investigation of pelvic fracture in pregnancy. This is surprising when one considers the effect of deformity brought about by unsatisfactorily united pelvic bones on women of the childbearing age, as well as the medicolegal implications regarding future pregnancy.

Since the time of Bandl,⁵ in 1875, and DeLee,² in 1904, many cases of non-penetrating traumatic rupture of the uterus during pregnancy have been reported. Elias,³ in 1950, reported a case of rupture of the pregnant uterus due to external violence, in which the fetus suffered a fracture of the fifth cervical vertebra. The bony pelvis of the mother was not injured. Orthner,¹¹ in 1933, pointed out that because the fundus of the pregnant uterus lies unprotected by the bony pelvic framework, it is the part most susceptible to rupture. The vascularity of the uterine wall directly beneath the placenta renders this the weakest point during the last trimester of pregnancy. According to DeLee and Greenhill,² a healthy uterus will tear only under the most violent trauma.

While Shuman, after reviewing 170,000 delivery records at the New York Lying-In Hospital, covering the period from 1890 to 1932, reported only one case of fractured pelvis (delivered spontaneously), Nolan and Conwell, in 1930, stated that 50 per cent of the total civilian cases of fracture of the pelvis occur in women. In 1937, Eliason and Johnson set the figure at 44 to 50 per cent, stating that the percentage may be expected to rise not only because of increasing automobile travel but also because of the large migration of women to men's industrial jobs.

It is known that the female pelvis is more fragile than that of the male. According to Voegelin and McCall, 10 the most common sites of fracture of the pelvis are the rami of the pubis and ischium and the alae of the ilium. Although these fracture victims are frequently rear seat automobile passengers who are forcibly thrown against the side of the car, in the cases to be reported one woman was driving, another was sitting next to the driver, and a third was struck while standing on the highway.

One cannot predict the immediate effect of violent trauma to the bony pelvis of the pregnant woman. While there is a possibility of the initiation of immediate abortion or premature labor, the injury may cause only shock without disturbing the pregnancy in any way. From an obstetrical point of view the importance of fracture of the pelvis lies in the possibility of distortion as it relates to future pregnancy or the conduct of labor in already pregnant patients. Although some severe pelvic fractures may heal without excessive callus formation or deformity, this is not always the case. Distortion of the pelvic inlet is likely to result from lateral crushing injuries, whereas marked displacement due to fracture of the rami of the pubis may seriously interfere with the pelvic outlet. If separation or displacement about the symphysis occurs, descent of the presenting part in labor may initiate injury to the urethra or bladder.

The degree of distortion, the size of the baby, and the interval since the fracture occurred will determine to a great extent the conduct of labor. Voegelin and McCall¹o reported 3 cases of pelvic fracture in pregnancy, all with subsequent vaginal delivery. They stressed the opinion that operative delivery should be the exception rather than the rule. Although, as Shuman³ reminded us, internal injury does not necessarily follow every fracture of the female pelvis, McCarty and Risley⁵ recently reported a case of traumatic rupture of the uterus accompanied by multiple fractures. They warned that intra-abdominal hemorrhage must always be kept in mind and strongly advocated immediate laparotomy when this complication is suspected.



Fig. 1.—Case 1. Osseous callus formation of pelvic fractures.

Case Reports

Case 1.—On Jan. 17, 1956, a gravida iii, para ii, semicomatose Indian woman, 25 years of age, was admitted to the hospital, after having been involved in an automobile accident. She was the driver of the vehicle, unaccompanied by anyone. Because of the patient's condition, a history was unobtainable. The blood pressure on admission was 90/60. Laboratory examinations showed the urine to be normal with no evidence of red blood cells; the hemoglobin 78 per cent (12.8 Gm.); and the hematocrit 36 per cent.

Physical examination showed the patient to be approximately six to seven months pregnant. The abdomen was soft and the fundus of the uterus was elevated about 24 cm. above the symphysis pubis. Fetal heart tones of good quality and a rate of 148 per

248

minute were heard in a movable fetus. Pelvic examination showed a normal vagina and uneffaced cervix; no vaginal bleeding was seen. The patient reacted to painful stimuli; conjugate deviation was evident; the right pupil was larger than the left; deep tendon reflexes were intact; and bilateral Babinski and Oppenheimer signs were observed. Immediate x-rays of the chest and skull were negative. Treatment consisted of emergency shock measures. It was decided to follow through with conservative surgical and obstetrical treatment without terminating the pregnancy.

Fig. 2.



Fig. 3.

Fig. 2.—Case 2. Fractured pelvis before delivery. Fig. 3.—Case 2. Fractured pelvis after delivery.

The patient remained in a critical state, the temperature on January 22 rising to 102° F. with rapid, shallow respirations. Supportive therapy was maintained and not until February 11 did the patient recognize her mother. At this time, uncoordinated movements along with a blank facial expression were manifest. The temperature continued to fluctuate between 99° and 103° F. until March 24. Fecal and urinary incontinence persisted.

On February 14, when her general condition began to show some improvement, x-rays of the pelvis were taken. A fracture of the right acetabulum extending to the posterior lip was visualized, as were fractures at the base of the superior pubic ramus and through the inferior pubic ramus. All fragments were in satisfactory position. A small amount of osseous callus formation had taken place at the acetabulum and pubic ramus sites (Fig. 1).

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unt ites On March 28, with no observed signs of labor, the patient delivered a normal infant spontaneously. The postpartum course was normal.

After delivery the patient continued to improve and physiotherapy was begun. She was allowed to get up at the beginning of April and on April 29 was discharged to the care of her mother.

Case 2.—On June 22, 1956, a 19-year-old Indian woman, gravida i, para 0, was admitted to the orthopedic service of the hospital. She gave the following history: Twenty-four hours previously she had been standing on the highway and did not notice a truck moving in her direction until it was almost upon her. The vehicle struck her, knocking her down and passing over her body. Some low-lying part beneath the truck struck her abdomen in the right lower quadrant and hit the right side of the pelvis.

The blood pressure on admission was 114/80. Immediate analysis of a catheterized urine specimen was not significant. Physical examination showed a normal soft, nontender abdomen, the fundus of the uterus rising about 29 cm. above the symphysis. A 10 cm., slightly swollen contusion was visible at the right lower quadrant. Any manipulation of the hips caused excruciating pain. Touch tenderness was elicited in the right lower quadrant and over the entire sacrum, as well as at a point on the crest of the right ilium. Upon pelvic examination the fetus was found to be in vertex position, left occiput anterior presentation, the head engaged. The amniotic membranes were intact and the cervix was posterior and undilated. The fetal heart rate was 144 and regular. The gestation was calculated to be of approximately eight months' duration.



Fig. 4.—Case 3. Pelvic deformity and callus formation before pregnancy.

Immediate x-rays showed subluxation of the right sacroiliac articulation and fracture of the superior ramus of the left ischium and inferior ramus of the left pubis (Fig. 2). The fragments were displaced slightly downward. In order that orthopedic treatment might be instituted, the patient was transferred to the obstetrical service for possible cesarean section or induction of labor.

On June 29 it was decided to give the patient a trial of labor and Pitocin was started. Contractions began, within two hours the membranes ruptured, and she was delivered spontaneously of a living infant. The postpartum course was normal.

The patient was retransferred to the orthopedic service on July 3, when x-rays of the pelvis were again taken. No change in alignment was found. She was placed in a pelvic sling for four weeks. Following release of traction the roentgenological examination showed no change in the subluxation of the right sacroiliac articulation but accentuation of the asymmetry of the symphysis pubis. Considerable osseous callus formation had taken place around the superior pubic ramus only (Fig. 3).

On July 30 the patient was discharged to the Reservation with a sacroiliac corset and followed in Orthopedic Clinic.

CASE 3 .- A 17-year-old girl who had been riding in the front seat of an automobile involved in a head-on collision was admitted to the hospital in May, 1951. Upon arrival the patient was unconscious. Lacerations of the scalp and multiple abrasions and contusions of the body as well as bleeding from the vagina were obvious. Immediate x-rays showed fractures of the first and second left ribs and of the distal end of the left clavicle. Also visualized were fractures of the inferior and superior ramus of the right pubis with considerable separation and displacement. The ramus of the left pubis also had multiple fractures but remained in good position. A laceration of the anterior vaginal wall and punctured bladder were diagnosed upon pelvic examination.

The patient responded well to emergency measures and subsequent surgical treatment. The position of the ramus of the right pubis did not change appreciably, however, the displaced fragments healing in that condition (Fig. 4).

Two years later the patient became pregnant. In May, 1954, an elective cesarean section was performed because the pubic deformity had narrowed the pelvis to a degree that rendered vaginal delivery impossible.

Observations

In Case 1, because of the patient's general condition, she was confined to bed and the pregnancy was permitted to run a normal course, which terminated in a full-term spontaneous delivery. A satisfactory healing of the fractured pelvis took place. In Case 2, on the contrary, in order to foster better healing of the fractured pelvic fragments, the pregnancy was interrupted. The results were less encouraging, as a pelvic deformity resulted. A future pregnancy will most likely necessitate cesarean section. As a point of interest, it may be conjectured that the pregnant uterus and its physiological forces acted as an internal pelvic splint, which functioned more adequately than the traditional artificial external pelvic splint or sling. In neither case, in spite of severe impact, did rupture of the uterus occur, possibly because the amniotic fluid serves as a cushion to absorb external shock. In Case 3, although the patient was not pregnant at the time of the accident, a pelvic deformity resulted, which, two years later, necessitated a cesarean section for delivery of the patient's first baby.

Summary

- 1. Three cases of fracture of the pelvis in women have been presented, two in pregnant women.
- 2. The constant uterine contractions and the pressure of the amniotic fluid during pregnancy seem to splint the fractured pelvis and foster better healing.
- 3. In such cases cesarean section or interruption of the pregnancy is not advocated as a routine procedure.
- 4. Rupture of the uterus must be considered in all cases of traumatic fracture of the pregnant uterus.

I wish to express thanks to Dr. Randolph Seligman, Albuquerque, New Mexico, for permitting publication of Case 3.

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RUPTURE OF THE UTERUS*

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A RECENT case of spontaneous rupture of the uterus stimulated our interest in this subject. A perusal of the literature and a review of all the cases, spontaneous and traumatic, which have occurred over the past twenty-six years at the Elizabeth Steel Magee Hospital, were undertaken in an effort to ascertain how certain questions can best be answered:

- 1. Is the incidence increasing or decreasing?
- 2. Is a ruptured uterus as lethal as generally considered?
- 3. What factors are involved in its occurrence?
- 4. How can such cases best be handled?

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Incidence

The reported incidence of ruptured uterus varies from a high of one in 95 deliveries at the Peking Union Medical College Hospital³² to a low of one in 3,173 deliveries at the Crawford W. Long Memorial Hospital in Atlanta as reported by Daniel and Inman.⁷ Considering another aspect of the situation Dugger¹⁰ found that 6.6 per cent of the total maternal mortality in Philadelphia over a 10 year span was caused by rupture of the uterus, and Eastman¹¹ estimated that 5 per cent of all maternal deaths are due to this cause. Table I shows the incidence as reported by various authors.

TABLE I. REPORTED INCIDENCE OF RUPTURED UTERUS

AUTHOR	PERIOD	CITY	NO. OF CASES	RATIO TO DELIVERIES
Whitacre and Fang ³²	1922-41	Peking	44	1:95
Sadowsky25	1929-38	Jerusalem	13	1:698
Beacham ³	1913-50	New Orleans	96	1:1,328
Tollefson ²⁹	1934-44	Los Angeles	14	1:1,370
Voogd, Wood, and Powell30	1943-55	Cleveland	12	1:1.432
Morrison and Douglass ²³	1920-43	Baltimore	45	1:1,465
Brierton ⁵	1932-46	New York	57	1:1,961
Fitzgerald14	1928-47	Chicago	42	1:2,196
Posner24	1935-49	New York	14	1:2,724
Bill*	1925-41	Cleveland	23	1:2,756
Dugger ¹⁰	1934-44	Philadelphia	105	1:3,029
Daniel and Inman?	1946-51	Atlanta	9	1:3,173

At the Elizabeth Steel Magee Hospital during the 26 year period from Jan. 1, 1930, to Jan. 1, 1956, there were 96,153 deliveries. During this time there were 37 instances of ruptured uterus in patients five months or more

^{*}Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Oct. 1,

pregnant, or an incidence of one rupture to 2,598 deliveries. If this time is divided into two 8 year periods and the 10 year postwar period, the incidence is as shown in Table II. As can be seen, the incidence in the postwar years has dropped rather sharply in spite of an increase in the number of deliveries.

TABLE II, RUPTURED UTERI AT ELIZABETH STEEL MAGEE HOSPITAL

PERIOD	NO. OF CASES	NO. OF DELIVERIES	RATIO
1930-37	9	20,621	1:2,291
1938-45	12	26,103	1:2,175
1946-55	16	49,429	1:3,089
1930-55	37	96,153	1:2,598

Age and Parity

In our series the largest number of cases fall in the age group from 26 to 30. Only 9 patients were under 26, while 28 were over. The oldest was 44. This increased age goes along with increased parity, as rupture of the uterus is less frequent in the primigravida and rises as the parity and age increase. For instance, Whitacre and Fang³² reported only 2 primigravidas in 44 cases, Ingram¹⁷ one in 13, Sadowsky²⁵ none in 13, Tollefson²⁹ one in 14, Posner²⁴ 2 in 14, Bill⁴ 3 in 23, Gordon¹⁵ 7 in 64, and Dugger¹⁰ 16 in 105. Taylor,²⁸ on the other hand, found 8 primigravidas in 33 cases of ruptured uterus. About half of our patients were gravida iv or over. Increased parity is generally accompanied by a more serious prognosis, and only one of our patients who were gravida vii or over survived while Dugger¹⁰ had no survivals among the 16 gravida vii or over in his series.

TABLE III. AGE AND GRAVIDITY

AGE	NO.	GRAVIDITY	NO.
20	3	i	4
21-25	6	ii	11
26-30	14	iii	4
31-35	7	iv	9
36-40	6	v	4
44	1	vi-xi	5

Classification

Classifications of ruptured uterus are many, such as cesarean and noncesarean, traumatic and spontaneous, complete and incomplete, primary and secondary. The most rational classification seems to us to be: (1) ruptured uterus in a previously intact uterus without apparent cause, i.e., spontaneous or idiopathic. Table IV shows our cases classified in this way; (2) ruptured uterus following previous uterine surgery, i.e., cesarean section, myomectomy, salpingectomy; (3) ruptured uterus following trauma, i.e., manual dilatation of the cervix, version and extraction, forceps, destructive operations, external violence, Pitocin, etc.

TABLE IV. CLASSIFICATION OF RUPTURED UTERI

	1930-37	1938-45	1946-55	TOTAL	%
Previous surgery	6	4	10	20	54.0
Traumatic	3	7	5	15	40.5
Spontaneous	0	1	1	2	5.5

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Spontaneous or Idiopathic Rupture.—It can be seen that spontaneous rupture of a previously intact uterus is an unusual occurrence. Only 2 cases (5.5 per cent) have been found at the Magee Hospital over the past 26 years. This is in accord with the findings of Gustafson¹⁶ who called such cases "very rare." Felmus¹³ in a recent review of the literature was able to find 116 cases to which he added 5. He concluded that there were 6 underlying entities which might be the cause of or a factor in spontaneous rupture of the uterus, namely: (1) history of curettage or manual removal of the placenta; (2) infection; (3) multiparity; (4) infarction of the myometrium; (5) excessive proliferation of chorionic epithelium or deficiency of uterine decidua; (6) adenomyosis.

One of our uteri showed deep penetration of the chorionic villi at the site of rupture and we presume this to have been the cause. Meyerhardt²² reported a spontaneous rupture of the uterus accompanied by placenta accreta while McCarthy²¹ reported one caused by placenta percreta. Irving and Hertig¹⁸ in a review of cases of placenta previa found only 4 spontaneous ruptures due to chorionic villi penetrating the visceral peritoneal surface of the uterus.

Our second patient was a 40-year-old gravida viii with a breech presentation and a normal-sized baby. After a labor of 9 hours she was brought into the hospital in deep shock and the baby was not delivered until after the mother had died. This elderly multigravida was obese and had an old scarred cervix which tore. Such patients are good candidates for a ruptured uterus.

Most cases of spontaneous rupture occur in the last trimester, but they may occur as early as the fourth month.¹³ The diagnosis is usually missed or confused with that of abruptio placenta. One of our 2 mothers died but both infants were stillborn. Felmus¹³ reported a maternal mortality of 55.9 per cent.

Rupture Following Previous Uterine Surgery.—Previous surgery on the uterus accounted for 20, or 54 per cent, of our 37 cases. The average gravidity was 3.4 and the average age 29 years. Table V shows the details of our cases.

TABLE V. RUPTURE FOLLOWING PREVIOUS UTERINE SURGERY

AGE (YEARS)	GRAVIDITY	TYPE OF PREVIOUS SURGERY	TERM (MONTHS)	MATERNAL OUTCOME	FETUS
1946-1955.—					
24	iv	3 classical sections	81/2	Well	Well
30	ii	1 classical section	8	Well	Stillborn
31	ii	Salpingo-oophorectomy	5	Well	Stillborn
25	ii	1 classical section	83/4	Well	Stillborn
39	v	2 classical sections	71/2	Well	Stillborn
31	ii	1 low cervical section	9	Well	Well
28	ii	1 low cervical section	81/2	Well	Well
30	iv	2 classical sections	83/4	Well	Stillborn
29	ii	1 classical section	83/4	Well	Well
29	ii	1 low cervical section	81/2	Well	Well
1938-1945					
26	iii	1 classical and 1 cervi- cal section	9	Well	Stillborn
26	iii	1 classical section	81/2	Well	Stillborn
26	ii	1 classical section	9	Well	Stillborn
30	ii	1 classical section	81/4	Died	Macerated
1930-1937.—					
23	iii	1 classical section	9	Well	Lived 7 hours
23	v	2 classical sections	81/2	Well	Stillborn
24	vi	3 classical sections		Well	Stillborn
38	xi	2 classical sections	8 7	Well	Stillborn
34	ii	1 classical section	61/2	Well	Lived 6 hours
31	iv	Myomectomy	9	Died	Stillborn

All complete ruptures of the uterus were in patients who had had previous classical cesarean section, except for one cornual rupture following salpingectomy and a complete rupture following a previous myomectomy. There were 4 occult or incomplete ruptures, 3 of which followed low cervical sections. All of these were incidental findings at operation. One patient had 2 successive complete ruptures of classical cesarean scars, and one patient who had previously had both a low cervical and a classical section suffered rupture at the latter site. Thus 14 complete ruptures of the uterus occurred in classical scars and only 3 ruptures, all incomplete, were through low cervical scars.

This is in general accord with the present-day concept that low cervical sections are safer, particularly in regard to future rupture. Fitzgerald¹⁴ reported 2 ruptures after low cervical section as opposed to 9 after classical sections, Bill⁴ none as opposed to 13, Acken¹ one as opposed to 7, Beacham³ 3 as opposed to 20. Brierton⁵ quoted an incidence of 2.8 per cent of rupture of the uterus following cesarean section, with 4.2 per cent following classical section and 1.9 per cent following low cervical section. Lund¹⁹ stated that 90 per cent of ruptures of scars follow the classical type of section.

This seems to confirm the view held by many and adhered to by us that classical cesarean sections should be limited to the few specific instances in which speed is essential or where technical difficulties prevent a low cervical

section.

The maternal mortality following complete rupture of a uterine scar in this series was 12.5 per cent. However, of the 16 babies only 2 survived, giving a fetal mortality rate of 87.5 per cent. One of the survivors was an infant whose mother's uterus ruptured as she was being prepared for operation.

We also feel that since there is no way to gauge how well a uterine incision will heal, or which one will rupture, the risk, especially for the fetus but also for the mother, is too serious to justify vaginal delivery following cesarean section except in unusual circumstances. This is true after classical sections and particularly if x-ray shows the placenta to be located under the previous scar. Accordingly, we do not subscribe to the recent trend^{2, 6, 17, 26} of encouraging vaginal delivery following a previous section. West³¹ "firmly believes" in the dictum, "once a section always a section." So-called "watchful expectancy" in the handling of a patient in labor following a previous section sounds well but too often it can be disastrous as far as the patient or her infant is concerned.

Traumatic Uterine Rupture.—Trauma as a cause of uterine rupture accounted for 40.5 per cent of our cases. The average gravidity was 3.7 and

the average age 29 years.

Internal podalic version and extraction and Braxton Hicks version accounted for all of our traumatic ruptures (Table VI). Bandl's ring was present in 5, manual dilatation of the cervix was admitted in at least 2, attempted forceps occurred in at least 2 instances. However, with care and strict adherence to contraindications we have had no fatal case of rupture of the uterus following internal podalic version and extraction in the last twelve years. In 1954 I¹² reported a series of 1,146 consecutive internal podalic versions and extractions in this institution with only 4 ruptured uteri.

The maternal mortality following traumatic rupture of the uterus was 53 per cent and the fetal mortality 53 per cent. It should be noted that the maternal death rate in this group was 100 per cent from 1930 to 1937, 58 per cent from 1938 to 1945 and only 20 per cent from 1946 to 1955. We had no ruptured uteri from other forms of trauma although Pituitrin was a factor in

one case which was handled terminally by Braxton Hicks version. Gordon¹⁵ reported 20 cases of ruptured uterus caused by version and extraction and 21 by forceps, craniotomy, fundal pressure, Pinard's maneuver, bagging, and Pituitrin. Many reports⁴, ¹⁵, ¹⁵, ²³, ²⁵, ²⁵ of rupture following the latter drug have appeared, as well as a case following an auto accident,³³ and one caused by injuries sustained in falling downstairs while drunk.¹⁴

TABLE VI. RUPTURE FOLLOWING TRAUMA

AGE (YEARS)	GRA- VIDITY	TYPE OF TRAUMA	TERM (MONTHS)	REASON	MOTHER	FETUS
1946-1958	5.—					
29	iv	Version and extraction	9	Neglected trans- verse presenta- tion	Well	Stillborn
39	vii	Manual dilatation of the cervix, Pituitrin, Brax- ton Hicks version	9	Unrecognized rup- ture. Not deliv- ered	Died	Stillborn
40	iv	Version and extraction	9	Transverse presentation	Well	Living
26	iv	Version and extraction	8	Transverse presentation	Well	Living
31	iv	Version and extraction	83/4	Failed forceps. Persistent occiput posterior	Well	Stillborn
1938-194	5.—					
24	i	Manual dilatation of the cervix, version and extraction	9	Labor 79 hours	Well	Lived 20 hours
44	x	Version and extraction	9	Brow presentation	Died	Stillborn
25	iii	Version and extraction	9	2 previous versions and extractions	Well	Living
20	V	Voorhees bag, version and extraction	$7\frac{1}{2}$	"Tough cervix"	Died	Living
20	V	Version and extraction	8		Died	Living
31	i	Version and extraction	9	Inertial labor 44 hours	Died	Living
20	i	Version and extraction	9	Inertial labor 48 hours	Well	Living
1930-1937	7.—					
26	i	Attempted forceps, version and extraction	9	Inertial labor 35 hours	Died	Stillborn
36	iv	Braxton Hicks version	9	Placenta previa	Died	Macerated
30	ii	Version and extraction	9	Transverse arrest	Died	Stillborn

Signs and Symptoms

These may vary from mild vague discomfort to severe pain and profound shock. Sometimes a patient is not even suspected of having a ruptured uterus, it being discovered at repeat section as an incidental finding. However, one must keep in mind rupture of the uterus if a patient has had previous uterine surgery, if she is in the last trimester of pregnancy, if pituitary extract has been given, or if the duration of labor has been unduly prolonged with failure of descent despite good contractions and a normal presentation.

The most common entity is shock. If shock follows external violence or a difficult delivery, the diagnosis is fairly clear. After every difficult vaginal delivery the uterus should be explored to rule out possible rupture. This is especially true after version and extraction, breech extraction, and mid- or

high midforceps. Again, if the patient in labor suddenly feels a severe tearing pain and utters a sharp cry, the diagnosis of ruptured uterus can be made without the physician's even being in the room. The patient's sensations may give an important clue, as may otherwise unexplained maternal tachycardia during labor. After rupture, the labor pains cease, the fetal heart sounds disappear, hemorrhage, external as well as internal, usually occurs, and often there is a complaint of suprapubic pain. We have not found tenderness of the scar to be especially significant.

When the patient is not in labor the diagnosis made is usually separation of the placenta. This may cause delay in operation, especially if the heart sounds have disappeared, as happened in our last fatal case which occurred in 1948

Mortality

Mortality figures as reported by various authors are listed in Table VII. Maternal mortality varies from 8.4 to 61 per cent, while fetal mortality varies from 33 1/3 to 93 per cent.

TABLE VII. MATERNAL AND FETAL MORTALITY

AUTHOR	NO. OF CASES	MATERNAL MORTALITY (%)	FETAL MORTALITY (%)
Dugger ¹⁰	105	61.0	62.0
Whitacre ³²	44	56.8	93.1
Fitzgerald14	42	54.7	79.0
Lynch ²⁰	33	53.0	88.0
Beacham ³	96	47.9	79.6
Delfs ⁸	53	47.1	81.1
Acken ¹	15	46.6	46.6
Morrison ²³	45	42.2	77.7
Bill4	23	22.0	62.0
Daniel ⁷	9	11.1	33.3
Voogd30	12	8.4	58.3
Present Series			
1930-37	9	44.4	100.0
1938-45	12	50.0	58.3
1946-55	16	6.2	56.2
Total	37	29.7	62.2

Three of our patients who died were admitted moribund, or died undelivered, and one died, through an error of judgment, on her way to the operating room for the second time. Nine patients died of shock and 2 of peritonitis.

Treatment

From analysis of our cases and those of other authors there seems to be no question but that immediate laparotomy combined with blood transfusion is the sine qua non of the treatment of ruptured uterus. This implies that Type O Rh-negative blood be available on a few minutes' notice in every delivery room and should be given immediately. Regardless of shock one should then proceed with laparotomy. There is a direct correlation between mortality and the time elapsed from rupture to operation. The amount of blood needed varies. Lund¹9 felt that 3,500 c.c. is the minimum amount required per patient. It seems to us that the amount must be fitted to the need of the individual patient; it is advisable, however, to have adequate blood available. Many of our patients did not receive sufficient blood.

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As to choice of procedure, hysterectomy or repair of the laceration can be done, depending on the nature of the laceration, the condition of the patient, the need for speed, the presence of infection, the type of delivery, etc. Laceration through a previous cesarean scar can be repaired, as a general rule. Table VIII shows how our patients were handled.

TABLE VIII. TREATMENT

	TOTAL	CASES					MATERNAL MORTALITY	
PROCEDURE	NO.	%	1930-37	1938-45	1946-55	NO. DIED	(%)	
Repair of laceration	13	35.1	3	5	5	1	7.7	
Hysterectomy	16	43.2	3	3	10	2	12.5	
Not operated upon	8	21.7	3	4	1	8	100.0	

It is interesting to note that of the 29 patients operated upon, only 3 died, whereas 8 died who were moribund on admission or who did not reach the operating room soon enough. This indicates a human error in either early diagnosis, failure of early transfusion, or delay in operation.

Very rarely, following delivery and rupture of the uterus, a patient will go into such profound shock that immediate operation cannot be tolerated. In such instances Dillon⁹ suggested immediate reflection of the anterior vaginal wall and bladder off the cervix and the placing of straight clamps on each cardinal ligament, followed by laparotomy when the patient can tolerate it. Also rarely, a case may arise where it would be more expedient to place clamps on the broad ligaments, remove the uterus, get out, and then remove the clamps about the third day.

Summary

At the Elizabeth Steel Magee Hospital over the past 26 years there have been 96,153 deliveries and 37 cases of ruptured uterus. This is an incidence of one rupture to 2,598 deliveries. In the last 10 years the incidence has fallen to one to 3,089. Most of the patients were over 25 years of age and all but 4 were multiparas. Two ruptures were spontaneous, 15 were traumatic, and 20 followed previous uterine surgery. The gross maternal mortality was 30 per cent and the fetal mortality 62 per cent. Rupture following previous uterine surgery had the lowest maternal mortality rate but the highest fetal mortality. In the last 10 year period the maternal mortality dropped to 6 per cent but the fetal mortality was 56 per cent. This probably can be accounted for on the basis of more conservative obstetrics with fewer difficult vaginal deliveries and more cesarean sections. In 13 cases the laceration of the uterus was repaired; in 16 hysterectomy was performed; and 8 patients never reached the operating room. Only 3 patients of the 23 operated upon died. All 8 of those not operated upon died.

Conclusions

- 1. Rupture of the uterus is becoming less frequent, but still carries a very high fetal mortality and a high maternal mortality.
- 2. Rupture following previous uterine surgery accounts for the greater percentage of cases, as traumatic deliveries are decreasing in number.

- 3. Previous classical cesarean section is adequate reason for repeat cesarean section, especially if the placenta is implanted under the scar.
- 4. The mortality varies in direct proportion to the elapsed time between diagnosis of the rupture and laparotomy.

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ABDOMINAL PREGNANCY

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ALTHOUGH abdominal pregnancy occurs infrequently, the incidence has increased since the advent of antibiotics. This increase is generally attributed to the fact that the modern treatment of pelvic inflammatory disease renders fewer women infertile but leaves more women with some form of tubal impediment.^{1, 2} Most authors feel that abdominal pregnancies are the result of tubal abortion, either partial or complete, with reimplantation outside the tube.^{2, 3, 4} The incidence of this gestational catastrophe varies directly with the incidence of pelvic inflammatory disease.^{1, 2, 5, 6}

Material

There were 3 abdominal pregnancies recorded in this Hospital from 1927 to 1951. The 11 cases reported here occurred during the years 1951 through April, 1956. The ratio of abdominal pregnancies to total deliveries on the clinic service was 1:782. No abdominal pregnancies occurred on the private service during this period. Therefore the ratio of abdominal pregnancies to total patients delivered would be 1:1,955. All abdominal pregnancies except one occurred in Negro patients and this would parallel our clinic incidence of Negro and white patients. Barrett, quoting the incidence of abdominal pregnancies to total deliveries, gives the high figure of 1:286. The range in occurrence of abdominal pregnancies reported is from 1:286 to 1:15,000.1, 5, 7, 8

The average age of this group of patients was 30 years. Six of them were primigravidas. The distribution according to period of gestation at the time of diagnosis was: 3 in the first trimester, 3 in the second trimester, and 5 in the third trimester. The diagnosis was made preoperatively in 8 out of 11 cases. These data are summarized in Table I.

Diagnosis

Most cases of abdominal pregnancy do not present a classical picture. Some of the signs and symptoms thought to be helpful in the diagnosis^{3, 5, 8} are: (1) an abdominal crisis early in pregnancy; (2) palpation of the superficial fetal small parts; (3) unusually loud fetal heart tones; (4) inability to palpate the round ligaments and absence of Braxton Hicks contractions; (5) "false labor"; (6) persisting abdominal pain or tenderness; (7) definite displacement of the cervix; (8) high position or transverse lie of the fetus; (9) signs of fetal death; (10) identification of an extrauterine mass.

Two ancillary aids helpful in making the diagnosis are the oxytocic extract test and hysterosalpingograms.^{9, 10} Some of the above listed findings, if present,

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TABLE I. HISTORY, PHYSICAL FINDINGS, AND LABORATORY WORK ON PATIENTS STUDIED

	_	-								PHYSICAL FINDINGS	FINDINGS		
						SYMPTOMS	SWC		CERVIX				HEMOGLOBIN
					LOWER	CESSATION			SMALL				NO
PATIENT	GR.	GRAV-	PARA	PARA GESTATION	ABDOMINAL		OF FETAL VAGINAL AND ACTIVITY BLEEDING VOMITING ANTERIOR	VOMITING		SMALL	DEAD	LIVING	ADMISSION IN GM. %
-	-	-	0	40	×			×	×		×		6.6
	98		0	32	×	×			н	M	×		10.5
	88	iv	iii	36	×	×					×		11.0
			0	42		×	×		×		×		7.9
		:::	0	39	×				×	×		×	5.9
			0	17	×			×	×		×		8.5
		•	iv	00	×		H			×	×		10.0
20.			:::	12	×		×			M	×		12.7
			0	12	×			×		×	×		7.1
	34	::1		19	×			×		×	×		10.2
		::	0	10	×		×	×		×	×		6.8

could serve to establish the diagnosis of an abdominal pregnancy, but all too often not enough of them are present, or the proper significance is not attached to them. The length of gestation also affects the probability of the presence of certain signs or symptoms. Obviously, however, the correct diagnosis of an abdominal pregnancy rests chiefly on a high index of suspicion on the part of the clinician. As a general statement, any pregnant patient whose clinical course does not conform to a "normal" pattern or who has unexplained abdominal pain with or without fetal death should be suspected of having an abdominal pregnancy.

The symptoms most frequently encountered in these 11 patients were (Table I): (1) lower abdominal pain; (2) cessation of fetal motion; (3) vaginal bleeding; (4) vomiting.

In the physical examination the following findings were helpful in the cases in which they were present: (1) a small cervix that was displaced anteriorly; (2) a small uterus or one not compatible with the length of gestation; (3) absent fetal heart tones.

Anemia of less than 9.5 Gm. of hemoglobin was present in more than one half of the cases. Three patients developed severe hypotension either during or immediately after an examination under anesthesia.

One of the easiest diagnostic tests available to differentiate intrauterine from extrauterine gestations is the oxytocic extract test. Colvin and McCord¹o first proposed this as a diagnostic test in 1934, using pituitary extract subcutaneously. Since the advent of Pitocin the test has been altered and can now be done with more safety as an intravenous infusion. A tokodynamometer makes this a relatively easy way of determining whether the patient is having uterine contractions.º We have seen good uterine contractile responses with intravenous Pitocin in patients who were only fourteen to sixteen weeks pregnant. The intravenous Pitocin did not cause abortions in any of the normally pregnant patients. This test was utilized on 3 patients with abdominal pregnancy and 6 suspected cases of abdominal pregnancy. Uterine contractions were palpated in all intrauterine gestations and none in abdominal gestations.

Management

There is some disagreement in the literature concerning the management of the patient with abdominal pregnancy. If fetal death has occurred, some authors^{3, 11} prefer to wait from seven days to eight weeks until the placental circulation decreases, minimizing the danger of hemorrhage at the time of operation. Others^{5, 7, 8, 12} feel that such delay results only in an increased susceptibility to infection with a resultant increase in the maternal morbidity and mortality. In these patients, when the diagnosis of abdominal pregnancy was established, laparotomy was immediately performed. Jeopardy to the patient's life comes from two causes—hemorrhage and infection. If operation is performed as soon as the diagnosis is made, the incidence of intra-abdominal infection is lowered.

It is known that approximately one third to one half of extrauterine fetuses will present some type of major or minor deformity.^{13, 14} It seems hardly logical to subject a patient to the hazards of procrastination only to succeed eventually in delivering a deformed child.

The management of the placenta does not begin after the fetus has been extracted but begins in the preoperative state. If an abdominal pregnancy has been suspected, adequate blood should be available. If, however, the diagnosis is not made until laparotomy, it is wise to wait until at least 4 units of blood are available to handle the immediate problem of delivery of the placenta. The vascularity of the placenta varies with viability and the location.^{1, 8, 5, 14} It

is impossible to make a dogmatic statement concerning the management of the placenta. Each case must be taken individually and managed in relation to the problems at hand after the fetus has been extracted. This decision is important and should be decisive—either an attempt to remove the placenta is made or it is left in situ. The decision has to be influenced by the location of the placenta and the condition of the patient, together with the availability of whole blood. It is unwise to attempt too much manipulation of the placenta unless it has been definitely decided to remove it. If it is to be removed, one of the best means of controlling hemorrhage is by pressure either at the bleeding site or directly on the aorta and other large vessels in the area. Burch¹⁵ used an aortic clamp to obtain adequate hemostasis. The same end result can be obtained if an assistant uses digital compression of the aorta against the vertebral column. Such aortic compression will be of value only if the parasitic blood supply of the placenta arises below the level of the renal vessels. After removal of the placenta bleeding from the vascular bed can be controlled by hot laparotomy tapes and by Gelfoam.

TABLE II. MANAGEMENT AND SUBSEQUENT COURSE OF PATIENTS STUDIED

PATIENT	PREOPERATIVE DIAGNOSIS	OPERATION	BLOOD REPLACEMENT (C.C.)	SUBSEQUENT . SURGERY	MORBIDITY IN DAYS
J. J.	Abdominal pregnancy	Fetus removed	4,000	Multiple col- potomies	40
E. W.	Toxemia with uncontrolled hypertension	Fetus and placenta removed. Pan- hysterectomy	2,000	None	8
M. T.	Ruptured uterus	Fetus removed	None	None	None
G. H.	Intrauterine	Fetus and pla- centa removed	1,000	None	None
В. Н.	Abdominal pregnancy	Fetus removed	1,500	Evisceration closure. Sec- ondary re- moval of placenta	60
M. V.	Abdominal pregnancy	Fetus and pla- centa removed	2,500	None	None
H. D.	Abdominal pregnancy	Fetus and pla- centa removed. Panhysterectomy	1,000	None	None
R. S.	Ectopic pregnancy	Placenta and fetus removed	500	None	None
G. T.	Abdominal pregnancy	Fetus and pla- centa removed	500	None	None
J. M.	Abdominal pregnancy	Fetus and pla- centa removed	5,000	None	None
E. A. W.	Abdominal pregnancy	Fetus and pla- centa removed	2,500	None	None

If the placenta is not removed one is faced with the delayed effects of a foreign body in the abdominal cavity. Some authors^{2, 8, 16, 17} advocate that nothing be done with the placenta, on the assumption that spontaneous resorption will take place. Other authors^{5, 8, 18-22} report in increased morbidity when the placenta is left in situ. The latter has been our experience (Table II). Two of the patients from whom the placenta was not removed during the original operation required prolonged hospital stays and additional operations. Each of these patients had a protracted septic course. The average stay of the patient whose placenta was left in situ was 51 days, in contrast to 13 days for those from whom the placentas were removed (Table III). No maternal death occurred in this whole group of patients and only one living child was delivered.

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TABLE III. SUMMARY OF 11 ABDOMINAL PREGNANCIES

Average age	30 years	
Parity		
Primigravidas	6	
Multigravidas	5	
Race		
Negro .	10	
White	1	
Length of gestation		
First trimester	3	
Second trimester	3	
Third trimester	5	
Preoperative diagnosis		
Correct	8	
Incorrect	3	
Average hemoglobin	9.2 Gm.	Range 5.3 to 12.7 Gm.
Average blood replacement	1,863 c.c.	Range 0 to 5,000 c.c.
Postoperative hospital stay in days	_,_ 00 000	,
Placenta in	51	
Placenta out	13	

Summary

- 1. Eleven abdominal pregnancies are reported.
- 2. A high index of suspicion resulted in the correct preoperative diagnosis in 8 of the cases.
- 3. The most common findings were abdominal pain, cessation of fetal motion, vomiting, anterior displacement of the cervix, and unexplained anemia.
- 4. Once the diagnosis was established, immediate laparotomy was the treatment of choice in this series. Adequate blood replacement prior to operation and the availability of at least 4 units of whole blood at the time of surgery are mandatory.
- 5. Management of the placenta must be individualized. In this group of patients there was a marked decrease in morbidity if the placenta was removed during the initial operation.
 - 6. No maternal deaths occurred and only one living child was delivered.

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THE SIGNIFICANCE OF THE SIGNS OF FETAL DISTRESS A Preliminary Study

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UNTIL recently, the welfare of the mother has been the main concern of the obstetrician. The past few years have seen a greatly increased interest in fetal outcome and in the manifestations of intrauterine fetal jeopardy. In addition to increased infant salvage, the prevention of brain damage has become increasingly important in the mind of the modern obstetrician.

A variety of obstetrical conditions have been mentioned by McCall,¹ Richardson,² and others^{3, 4, 5} as the causes of fetal distress. The studies of Lillienfeld⁶ and Latham⁷ indicate that fetal hypoxia is one of the causes of irreparable brain damage. Early recognition of the known signs of fetal distress which may indicate sublethal oxygen deprivation should aid in the prevention of this development. There are some instances in which no demonstrable reason for intrapartum jeopardy or even death is discovered. It may be, however, that in all instances the clinical manifestations of fetal distress are at some time sufficiently pronounced for recognition and decisive action, even though the ultimate causes for this distress may not become apparent.

As to the heart sounds, recent physiological studies by Barcroft,8 Greenfield,9 and Reynolds10 have shown that fetal distress due to anoxic factors is indicated by bradycardia, with transient or prolonged tachycardia during the recovery. Almost all authors agree as to the grave prognostic significance of a slow fetal heart rate. 11-17 On the other hand, a rise in the rate has been the subject of much controversy. It is considered important by some authors^{2, 11, 14-16} and is minimized by others.^{3, 12, 17} Fluctuation in the fetal heart rate is thought to be important by Beck15 and by King,12 while Abolins16 is concerned about qualitative changes in fetal heart sounds. As to the significance of meconium, Walker18 points out that marked hypoxia is necessary to produce this stain in the amniotic fluid, but controversial statements concerning the actual clinical significance of this sign have been made by Hunt,⁴ Adair,¹¹ and King.¹² DeSoldenhoff¹³ and White¹⁹ feel that meconium staining does not indicate severe distress unless it is accompanied by abnormalities in the fetal heart rate. In general, the newest studies by McCall, White, 19 De-Soldenhoff, 13 and Fitzgerald 20 suggest that very few babies die in the process of being born, or shortly thereafter, without first giving detectable warning signs. It is concerning the interpretation of these signs when considered separately and in combination that further information is required to effect an increase in fetal salvage and in subsequent health.

Recently, a review of the cesarean sections done for fetal distress at the Hospital of the University of Pennsylvania²¹ was undertaken in the effort to

determine the significance of the signs which seemed to warrant the abdominal delivery of patients who were not immediately deliverable per vaginam. Sixty-seven records were studied. Of the 72 babies in this series, 12 per cent were temporarily affected at birth, 7 per cent were stillborn, and 8 per cent succumbed during the neonatal period. A 15 per cent mortality rate occurred despite what, at the time, was considered to be adequate intrapartal observation and prompt intervention, when indicated.

It then seemed in order to conduct an intensive study of patients while they were in labor, in the effort to correlate the accepted signs of fetal distress with the condition of the newborn, both at birth and during the postnatal period. A further correlation is attempted between the signs of difficulty and the actual conditions that were found to account for these signs.

Materials and Methods

This study encompasses a 6-month period from July 20, 1955, to Jan. 20, 1956. The signs of distress which were selected for this study concerned the fetal heart rate, cardiac arrhythmias, and meconium staining in vertex presentations. The fetal heart tones were recorded at intervals of 15 to 30 minutes (or more often as indicated) in all but 5 per cent of the patients in this series. All who manifested any of the above signs, no matter how transient. were included in the study. The following data as to the signs were also recorded: (1) their relationship to contractions, (2) their duration, (3) the stage of labor in which they appeared, and (4) their transience or permanence. Causes found to account for the signs of fetal distress were listed as follows: (1) anatomical factors, including such items as cord and placental accidents, (2) dynamic factors including long labor and cephalopelvic disproportion, and (3) no factor discovered. The immediate neonatal condition is presented as: (1) infant not affected, (2) affected infant, and (3) stillborn infant. An affected infant was one with 3 or more minutes of neonatal apnea, poor muscle tone and color, who required more than the usual means of resuscitation. The condition of the newborn after 4 days was assessed from the point of view of weight loss, respiratory difficulty, neurological disturbance, and feeding problems. This is catalogued as: (1) good, (2) poor, and (3) neonatal death.

The total deliveries for the time period numbered 1,363, with 152 instances of possible fetal distress, an incidence of 11.2 per cent. The cases fell into the following categories:

1. Meconium staining alone			77	cases
2. Falling fetal heart rate			48	cases
(including 8 cases with rising also)				
(a) alone	33	cases		
(b) with meconium	15	cases		
3. Rising fetal heart rate			20	cases
(a) alone	11	cases		
(b) with meconium	9	cases		
4. Fluctuation in rate with meconium			7	cases

Results

The age and parity distribution of the patients in this series were the same as those of the general obstetrical population. Prematurity and post-maturity were not significant factors in that length of gestation was 38 to 42 weeks in 93 per cent of patients.

Meconium-stained Amniotic Fluid.—Table I depicts an analysis of the instances of meconium staining of amniotic fluid alone as a sign of fetal distress.

The recognition of this sign is dependent upon rupture of the amniotic membranes. The meconium appeared immediately after rupture in almost all cases. No difference was noted in the outcome whether it appeared at once or during subsequent hours. All the deliveries were vaginal except for one cesarean section for failed trial of labor. While numerically meconium staining alone did not signify fetal jeopardy, this sign was not entirely benign because 9 babies were affected at birth. There were 2 neonatal deaths: one within 2 days from multiple congenital anomalies incompatible with life, the other within 7 hours of birth due to respiratory failure. In the latter case, it was noted that the fetal heart sounds had been recorded at infrequent intervals during labor with no notation for 40 minutes prior to delivery. It is possible that significant fetal heart rate changes had occurred without having been noted.

TABLE I. MECONIUM STAINING ALONE IN VERTEX PRESENTATIONS

		CONDITI	ON OF NE			CONDITION OF NEWBORN FACTORS A FOR TH			S ACCOU		
	100	NOT AF-		STILL- BORN	GOOD	POOR	NEO- NATAL DEATH	TOTAL MOR- TALITY	ANATOM-	DY-	NONE
77	50	68	9	0	74	1	2	2	21	10	46

Factors to account for the meconium staining were present in 31 cases. The anatomical factors consisted of 18 cord accidents, 2 placental accidents, and 1 congenital anomaly. The dynamic factors were 7 long or precipitate labors, 2 instances of Pitocin spasm, and one of maternal anoxia due to prolonged laryngospasm. Even though most of the infants were not severely affected, the proportion of potentially dangerous factors was considerable. Meconium staining in vertex presentations means that the fetus is in distress at least transiently, and that the factors responsible for this occurrence may persist, or they may recur with increasing severity. Therefore, meconium staining alone should serve as a warning of potential fetal jeopardy, and thereafter the patients should be observed continually for other signs of fetal distress.

Fetal Bradycardia.—Table II depicts the cases with slowing of the fetal heart rate below 100 beats per minute. Forty-eight of the patients showed this sign, 15 with and 33 without meconium staining. Eight patients had the added sign of increased fetal heart rate either before or after the onset of the slowing. In 21 cases, the fetal heart rate dropped only with contractions and recovered in the interval phase. In the remainder, the slowing was continual. The fetal outcome was no worse in those cases in which the heart rate was continually slow. Furthermore, slowing with contractions did not necessarily indicate a demonstrable cord accident or abnormality. Fourteen of the 48 babies with bradycardia were markedly affected at birth, 2 were stillborn, and 2 died within 4 days. A greater proportion of affected babies and still-births was seen in the subgroup with the added factor of meconium staining. Also, a greater proportion of babies in poor condition after 4 days and of neonatal deaths occurred in this group.

Dynamic or anatomical causes for the potential fetal distress were found in 41 of the 48 cases. Anatomical causes were 16 cord accidents, 3 placental accidents, and one congenital anomaly. Dynamic factors were 8 cases of Pitocin spasm, 5 of cephalopelvic disproportion, 4 of long or precipitate labor, 2 of maternal hypotension, and 2 instances of pre-eclampsia. In this group,

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3 cesarean sections were done, 2 for fetal distress and one for abruptio placentae. The remainder of the babies were delivered vaginally, 18 of whom showed sufficient distress to prompt immediate delivery. In the rapid delivery group, 6 babies were affected at birth, 2 were stillborn, and 2 died within 4 days. The latter 4 deaths constituted the total mortality in the bradycardia group. Slowing of the fetal heart rate below 100 beats per minute indicates highly significant fetal distress and the added presence of meconium staining is still more significant. There is some suggestion that prolonged continuous, or recurrent intermittent slowing of the fetal heart rate may indicate a graver fetal outcome, but proof of this must await the use of a method for the continuous recording of fetal heart tones.

TABLE II. SLOWING OF FETAL HEART RATE

			CONDI	TION OF : BORN	NEW-		TION ON IN 4	F NEW-		FACTORS FOR	ACCOUNTHE SIGN	
	NO. OF CASES	% OF SERIES	NOT AF- FECTED		STILL- BORN	GOOD	POOR	NEO- NATAL DEATH	TOTAL MOR- TALITY	ANATOM- ICAL	DY-	NONE
Slowing alone Slowing with me	33	22	25	7	1	31	0	1	2	13	17	3
conium	15	10	7	7	1	11	2	1	2	7	4	4
Total	48	32	32	14	2	42	2	2	4	20	21	7

Fetal Tachycardia.—Table III shows the cases with increase of the fetal heart rate above 170 beats per minute. Twenty patients presented this sign, 9 with and 11 without meconium staining. The relationship to contractions did not appear to be important in the outcome. The fetal danger was far less significant than in the preceding group. There were no intrapartum or neonatal deaths. Five of the 20 infants were affected at birth, but only one was in poor condition after 4 days.

TABLE III. RISING FETAL HEART RATE

			CONDI	FION OF :	NEW-		TION O	F NEW- DAYS		FACTORS FOR	ACCOUNTHE SIGN	
	NO. OF CASES	% of SERIES	NOT AF- FECTED		STILL- BORN	GOOD	POOR	NEO- NATAL DEATH	TOTAL MOR- TALITY	ANATOM- ICAL	DY- NAMIC	NONE
Rising alone Rising with me	11	7	9	2	0	11	0	0	0	3	1	7
conium staining	g 9	6	6	3	0	8	1	0	0	2	2	5
Total	20	13	15	5	0	19	1	0	0	5	3	12

The anatomical factors were 4 cord abnormalities and one placental accident. The dynamic factors were 2 cases of cephalopelvic disproportion and one of long labor. In this group, there was one cesarean section for placenta previa. The remainder of the infants were delivered per vaginam, 7 rapidly because of the constantly rising fetal heart rate. The fetal outcome was uneventful even when rapid vaginal delivery seemed to be indicated. Rising of the fetal heart rate above 170 beats per minute does not signify severe distress. The presence of meconium staining, however, as an additional sign, may indicate some increase in fetal jeopardy.

TABLE IV. FLUCTUATION OF FETAL HEART RATE WITH MECONIUM STAINING

		CONDITI	ONDITION OF NEWBORD	WBORN	CONDITI	INDITION OF NE	EWBORN		FACTORE	FOR THE SIGNS	TTING
							NEO-	TOTAL			
TO. OF	% OF	NO. OF % OF NOT AF- AF-	AF-	STILL-			NATAL	NATAL MOR-	ANATOM-	DY-	
ASES	SERIES	CASES SERIES FECTED FECTED		BORN	G00D	POOR	DEATH	TALITY	_	ICAL NAMIC NONE	NONE
7	5	7	0	0	7	0	0	0	22	0	2

TABLE V. TOTAL CASES OF FETAL DISTRESS

	GNS	NONE	NO. %	44.1
	THE SI	NO	NO.	29
	NG FOR	MIC	%	22.4
	OUNTE	DYNAMIC	NO.	34
	ACTORS ACCOUNTING FOR THE SIGNS	NATOMICAL	NO. %	33.5
	FACT	ANATO	NO.	51
	TOTAL	MORTALITY	NO. %	3.9
	TOT	MORT	NO.	9
S	ATAL	DEATH	%	2.6
CONDITION OF NEWBORN IN 4 DAYS	NEON	DEA	NO.	4
BORN I		POOR	NO. %	5:6
OF NEW		PO		4
NOLLION (000B	NO. %	93.5
CONI		OĐ	NO.	142 93.5
		STILLBORN	%	1.3
ORN		STILL	NO.	63
OF NEWBOR		AFFECTED	%	18.4
TION OI		AFFE	NO.	28
CONDI	T	CTED	%	80.3
	TON	AFFE	NO.	122
		% OF	SERIES	100
		NO. OF % OF	CASES	152

Fluctuation in the Fetal Heart Rate.—Table IV shows a few instances of fluctuation in the fetal heart rate of 40 or more beats per minute with meconium staining. The fetal outcome was entirely uneventful in this group. Definite factors were present to account for the signs in most instances, however. All of the patients were delivered vaginally in a normal way. Fluctuation of the rate within the limits of 100 to 170 beats per minute does not appear to indicate significant distress.

Summary of Results.—The entire series is summarized in Table V. Of 152 patients with signs of fetal distress, 1.3 per cent of the babies were stillborn, 2.6 per cent died in the neonatal period, 18.4 per cent were affected at birth, and 2.6 per cent were in poor condition after 4 days.

Comment

A comparison of the Service infant wastage during this study period with that of this particular series is interesting. The incidence of intrapartum deaths in all deliveries was 0.3 per cent in contrast to the 1.3 per cent in this series. Following all the deliveries during the study period, the neonatal death rate was 1.2 per cent against the 2.6 per cent in this series. The total intrapartum and neonatal mortality for all deliveries was 1.3 per cent against 3.9 per cent in this series. These figures indicate the generally grave prognostic significance of the recognized signs of fetal distress.

A more diligent search for the signs of fetal distress might have resulted in the salvage of 4 of the 6 infants who died in this series.

In the entire study group, 55.9 per cent showed anatomical or dynamic causes for the fetal distress. They included cord accidents in 28 per cent, rapid or long labor and cephalopelvic disproportion in 12 per cent, Pitocin spasm in 7 per cent, and placental accidents in 5 per cent.

Summary

- 1. The signs of fetal distress occurred in 11.2 per cent of 1,363 deliveries.
- 2. Following these signs the total intrapartum and neonatal mortality was over twice that of the general population.
- 3. The most common factors to account for the signs of fetal distress were: cord accidents, labor defects, cephalopelvic disproportion, Pitocin spasm, and placental accidents.
- 4. Age, parity, prematurity, and postmaturity were not important factors in predisposing to fetal distress.
- 5. Meconium staining alone in vertex presentations indicates a generally favorable outcome, but it should warn one to be on the alert for the other signs of fetal distress.
- 6. Slowing of the fetal heart rate below 100 beats per minute indicates very significant fetal jeopardy. The presence of meconium staining as an additional factor indicates even more severe trouble.
- 7. An increased fetal heart rate above 170 beats per minute does not signify severe fetal distress, but the presence of meconium staining as an additional factor may indicate some increase in fetal jeopardy.

- 8. Fluctuation of the rate by 40 beats per minute within the limit of 100 to 170 with meconium staining does not appear to indicate fetal distress.
- 9. Prompt recognition of the signs of fetal distress and decisive intervention when necessary should prove fruitful in lowering both infant mortality and subsequent evidence of damage to the central nervous system. This is an area of obstetrics in which much can be done by careful intrapartal observation with our present knowledge and facilities until some means is devised by which fetal distress can be promptly and accurately diagnosed.

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THE COMBINED USE OF ALPHAPRODINE (NISENTIL) HYDROCHLORIDE AND LEVALLORPHAN (LORFAN) TARTRATE FOR ANALGESIA IN OBSTETRICS

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R ESPIRATORY and circulatory depression of the newborn is the most frequent and severe complication of the administration of drugs used for the production of analgesia and amnesia in obstetrics. This depression is caused partly by passage of narcotic analgetics^{1, 2} and of barbiturates³⁻⁵ across the placental barrier, and partly by the further decrease in the low fetal oxygen tension by the respiratory depression of the mother elicited by these agents.

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During the past few years, several workers investigated, both in animals and in man, the usefulness of the narcotic antagonist nalorphine in preventing and/or treating narcotic-induced respiratory depression in the newborn. Thus, Snyder⁶ reported that massive doses of alphaprodine (Nisentil) hydrochloride, a short-acting, potent narcotic analgetic, administered intravenously to mother rabbits, depressed respiratory movements of breathing fetuses within the unopened uterus following laparotomy, and that nalorphine injected into the maternal ear vein produced increased fetal respirations.

In man, the value of nalorphine in preventing respiratory depression of the newborn was demonstrated by Eckenhoff and others, who gave this antagonist intravenously in doses of 10 mg., usually 10 minutes prior to delivery, to mothers who had received meperidine, secobarbital, and scopolamine for sedation. Cappe and others found that a mixture of morphine and nalorphine produced good analgesia without respiratory depression of mother and infant. Eckenhoff and others and Paterson and Prescott showed that nalorphine injected into the umbilical vein of depressed newborn infants overcomes the respiratory difficulties produced by maternal sedation with narcotic analgeties.

Swerdlow and others¹¹ showed that in unanesthetized subjects another narcotic antagonist—levallorphan tartrate—prevents or overcomes alphaprodine-induced respiratory depression to a considerable degree if given in appropriate ratios before, together with, or after this analgetic. Similarly, Foldes

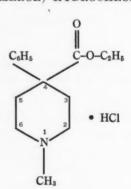
and others¹² reported that in anesthetized patients the combined use of alphaprodine and levallorphan (Lorfan) for supplementation of nitrous oxide-oxygen-thiopental sodium anesthesia largely prevents depression of respiration from this narcotic analgetic, without abolition of pain relief. These findings and the reports that alphaprodine is a valuable drug in combating labor pain^{13, 14} prompted us to study the effects of this analgetic combined with levallorphan in obstetrics.

ALPHAPRODINE

(NISENTIL) HYDROCHLORIDE

MEPERIDINE

(DEMEROL) HYDROCHLORIDE



1,3-Dimethyl-4-Phenyl-4-Propionoxy-

Piperidine Hydrochloride

1-Methyl-4-Phenyl-4-Carbethoxy-

Piperidine Hydrochloride

N-CH₃

H₂

Fig. 1.—Structural formulas showing chemical relationship between alphaprodine (Nisentil) hydrochloride and meperidine (Demerol) hydrochloride.

Fig. 2.—Structural formulas showing chemical relationships between the narcotic analgetics, levorphanol (Levo-Dromoran) and morphine, and the narcotic antagonists, levallorphan (Lorfan) and nalorphine (Nalline).

Alphaprodine, a piperidine derivative (1,3-dimethyl-4-phenyl-4-propionoxy-piperidine), which is closely related to meperidine (Demerol) (Fig. 1), was synthesized by Ziering and Lee in 1947. On a molar basis, alphaprodine is 2.5 to 3 times as potent as meperidine, and its duration of action is considerably shorter.

Levallorphan, a morphinan derivative (1-3-hydroxy-N-allylmorphinan), was synthesized by Schnider and Grüssner. It has the same structural relationship to levorphanol (Levo-Dromoran) as nalorphine (Nalline) to morphine (Fig. 2). Fromherz and Pellmont¹⁵ reported that, in animals, levallorphan antagonizes the respiratory effects of morphine and Levo-Dromoran. Similarly, Benson and others¹⁶ showed, in rabbits, that narcotic-induced depression of respiratory rate and volume is reversed by levallorphan.

Since the aforementioned clinical work with alphaprodine and levallorphan was carried out by intravenous administration and since alphaprodine is given to obstetrical patients subcutaneously, a preliminary study was undertaken in 10 healthy young women to determine whether the respiratory and circulatory effects of alphaprodine and levallorphan, given subcutaneously, are comparable to those following the intravenous administration of this combination. The results of this study¹⁷ indicated that a dose of 1 mg. of alphaprodine per kilogram of body weight and of 0.02 mg. of levallorphan per kilogram produced excellent analgesia and good sedation, with minimal or no depression of respiration or circulation.

Material and Methods

Two hundred white parturients (46 primiparas and 154 multiparas) were included in the study. Their ages ranged from 17 to 45 years, with an average of 28.8 years.

The prepregnancy weight of 97 patients ranged from 51 to 60 kilograms and that of 39 women each from 40 to 50 kilograms and from 61 to 70 kilograms, respectively. The prepregnancy weight of the remaining 23 parturients was over 71 kilograms.

When labor was well under way, as indicated by regular, painful uterine contractions and by dilatation of the cervix to at least 2 to 3 cm., the patients received subcutaneously a premixed solution of alphaprodine (40 mg. per milliliter) plus levallorphan (0.8 mg. per milliliter).* The initial dose, in terms of alphaprodine, was 1 mg. per kilogram of prepregnancy weight. The only other medication given at this time was 0.4 or 0.6 mg. of scopolamine hydrobromide which was administered intramuscularly. Mothers whose prepregnancy weight was under 55 kilograms received the smaller dose and those whose prepregnancy weight was over 55 kilograms, the larger dose. One-half the initial dose of the alphaprodine-levallorphan mixture was repeated as required, with the second injection spaced at least 30 minutes after the first. However, subsequent injections were administered at shorter intervals (15 to 20 minutes, if needed). Additional doses of 0.2 to 0.3 mg. of scopolamine were used occasionally in cases of prolonged labor.

^{*}The premixed solution of alphaprodine (Nisentil) hydrochloride (40 mg./ml.) and levallorphan (Lorfan) tartrate (0.8 mg./ml.) was supplied in 10 ml. multiple-dose vials through the courtesy of Dr. Leo A. Pirk of Hoffmann-La Roche, Inc., of Nutley, N. J.

The medications given, the size of each dose, and the number of doses, as well as the time intervals from the first alphaprodine-levallorphan injection to the induction of anesthesia, were recorded.

The total analgetic requirements of patients, grouped together in accordance with these time intervals, were averaged. Furthermore, the average milligrams per minute and micrograms per kilogram per minute alphaprodine requirements were calculated for these groups.

Observations made on the mothers included measurements of respiratory rate, pulse rate, and blood pressure which were carried out at 20 minute intervals. Fetal heart rates were determined at 20 minute intervals.

The degree of analgesia attained in a given patient was classified as excellent, good, fair, or poor as estimated by her over-all response to uterine contractions during the entire course of labor.

Patient cooperation was recorded as good or poor and the emotional state as apprehensive or relaxed, both before and after the first injection of the alphaprodine-levallorphan mixture. The level of consciousness of the parturients at the end of the first stage of labor was also noted, as was the duration of labor.

The average duration of labor in the primiparas and multiparas of the present series was compared with the corresponding figures for a control series of 300 patients who received other forms of analgetic medication such as meperidine hydrochloride and scopolamine; barbiturates and scopolamine; or barbiturates, meperidine, and scopolamine. These findings were correlated with those reported by other workers.

The occurrence of nausea and vomiting during labor was recorded.

The mode of anesthesia for delivery was saddle block in 159 and nitrous oxide-oxygen-ether in 40 patients. (One woman was delivered without anesthesia.)

Breathing and crying times of the babies (time intervals between completion of delivery, the first respiration, and the first lusty cry, respectively) were carefully recorded. The averages of these measurements in the two groups of infants born to mothers anesthetized with the previously mentioned techniques were compared with the corresponding averages determined for 200 infants of the control series, born to mothers of whom 100 each were delivered with saddle block or nitrous oxide-oxygen-ether anesthesia, but who had received other types of analgetic medication during labor (see above).

Similarly, the "Apgar score" was calculated for the infants in our series. The average scores, determined for the babies delivered from the groups of mothers who had received the two types of anesthesia, were compared with the figures reported by Apgar¹⁸ in groups in which the same modes of anesthesia had been employed.

The analgetic requirements of the postpartum patients were recorded and compared with those of a control series. The presence or absence of retrograde amnesia and the occurrence of side effects after delivery and of postpartum complications were noted.

All observations prior to and after delivery were made by the same observer (D. D. B.).

Results

One hundred and eight women, or 54 per cent, were given one or 2 doses of the alphaprodine-levallorphan mixture; 81, or 40.5 per cent, required from 3 to 6 doses, and 11, or 5.5 per cent, from 7 to 11 doses.

The total dose of the alphaprodine-levallorphan mixture, in terms of the narcotic analystic per patient, ranged from 48 to 330 mg. The smallest dose

was given to a multipara, aged 24, whose prepregnancy weight was 48 kilograms and the largest dose to a primipara, aged 27, whose prepregnancy weight was 60 kilograms and who was delivered of twins after she had been in labor for $22\frac{1}{2}$ hours. The levallorphan dose, which this patient received together with the alphaprodine, was 6.6 mg.

The time interval between the initial alphaprodine-levallorphan dose and the induction of anesthesia was 2 hours or less in 4 of the 46 primiparas, or in 8.6 per cent; it ranged from more than 2 hours to 12 hours in 34, or 73.9 per cent; and was more than 12 hours in 8, or 17.5 per cent. For the 154 multiparas the corresponding figures were 87, or 56.5 per cent; 65, or 42.2 per

cent; and 2, or 1.3 per cent.

It is evident from Table I that the average milligrams per minute and micrograms per kilogram per minute alphaprodine requirements were inversely proportional to the length of the time intervals between the first analgetic antagonist dose and the induction of anesthesia.

Table I. Relationship Between Alphaprodine Requirements and Time Intervals in Minutes From First Alphaprodine-Levallorphan Dose to Induction of Anesthesia 200 Parturients Receiving Alphaprodine-Levallorphan Mixture

	TIM	E IN M		FROM FIL							ORPI	IAN I	os	E
	< 30	31-60	61-120	121-180	183	1-240	241	-360	36	1-480	481	1-720	7	21+
Number of patients	18	29	44	28		24		25		9		13		10
Average prepregnancy weight (kg.)	57.6	61.6	59.7	58.2		58.7		60.2		64.0		59.1		57.1
Average total alphapro- dine requirements (mg.)	57.9 ± 0.0*	76.5 ± 4.9	87.6 ± 4.3	91.9 ± 6.7		29.0 9.4		32.9 7.5		174.1 15.5		201.9 16.3		222.3 18.4
Average milligram per minute alphaprodine requirements	2.8 ± 0.0	1.6 ± 0.1	1.1 ± 0.0	0.6 ± 0.0	<u>+</u>	$\begin{array}{c} 0.6 \\ 0.1 \end{array}$	±	$0.4 \\ 0.1$	±	0.4 0.0	±	0.3 0.0	±	0.2
Average microgram per kilogram per minute alphaprodine require- ments	51.0 ± 4.9	25.0 ± 1.8		10.0 ± 0.0	±	11.0 0.9	±	7.0 0.2	±	7.0 0.7	±	6.0 0.6		4.0 0.1

^{*}Standard error.

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he se The number of injections of scopolamine per patient varied from one to 8 and the total amount of scopolamine administered per patient ranged from 0.4 to 2.8 mg. (average 0.74 ± 0.02 mg.). The numbers of patients who received 1, 2, 3, 4, 5, and 8 doses of scopolamine were 159, 29, 7, 4, 4, and 1, respectively.

As is seen from Table II, the average changes of respiratory rate and systolic and diastolic blood pressures recorded for the 200 parturients were insignificant. However, there was a moderate rise of the average pulse rate.

Table II. Changes of Respiratory Rate, Pulse Rate, and Blood Pressure in 200 Parturients Receiving Alphaprodine-Levallorphan Mixture

READINGS	AVERAGE RESPIRATORY RATE	AVERAGE PULSE RATE	AVERAGE SYS- TOLIC BLOOD PRESSURE	AVERAGE DIAS TOLIC BLOOD PRESSURE
Initial	27.9	85.2	116.8	77.4
Minimal	26.5	79.9	110.5	72.5
Maximal	28.9	103.5	124.2	80.2
Terminal*	28.1	95.5	118.8	75.5

^{*}Before induction of anesthesia.

The figures in Table III indicate that analgesia was excellent in 81.5 per cent of the women, good or fair in 13.5 per cent, and poor in 5 per cent; that patient cooperation was good and the emotional state relaxed in all 200 patients after the first injection of the alphaprodine-levallorphan mixture; and that 61 per cent of the parturients were awake, 35 per cent lightly asleep, and 4 per cent deeply asleep at the end of the first stage of labor.

TABLE III. CLASSIFICATION OF ANALGESIA, PATIENT COOPERATION, EMOTIONAL STATE, AND LEVEL OF CONSCIOUSNESS OF 200 PARTURIENTS WHO RECEIVED ALPHAPRODINE-LEVALLORPHAN MIXTURE

		NO. OF PATIENTS	%
Degree of Analgesia.			
Excellent		163	81.5
Good		14	7.0
Fair		13	6.5
Poor		10	5.0
	Total	200	100.0
Patient Cooperation.			
Before drug ada	ministration:		
Good		194	97.0
Poor		6	3.0
	Total	200	100.0
After first alpha	prodine-levallorphan injection:		
Good	1 0	200	100.0
Poor		0	0.0
	Total	200	100.0
Emotional State.—			
Before drug adı	ministration:		
Apprehensiv	7e	23	11.5
Relaxed		177	88.5
	Total	200	100.0
After first alpha	prodine-levallorphan injection:		
Apprehensiv	ve -	0	0.0
Relaxed		200	100.0
	Total	200	100.0
Level of Consciousne	ss at End of First		
Stage of Labor			
Awake		122	61.0
Lightly asleep		70	35.0
Deeply asleep		8	4.0
	Total	200	100.0

Table IV lists the average duration of labor of 192 patients* who received the alphaprodine-levallorphan mixture, of the 300 patients of the control series who were given other analgetic medication not including a narcotic antagonist, and of representative series reported in the literature. It is evident that our figures compare favorably with those of other workers.

The incidence of nausea during labor was 3.5 per cent both in the present series and in the control series.

There were 198 single and 2 twin deliveries in the alphaprodine-levallorphan series.

The 200 patients were delivered of 201 live infants, and there was one stillborn child in whom the absence of heart sounds was first observed 90 minutes after administration of the preceding fractional dose of the alphaprodine-levallorphan mixture. The mother, a primipara, had been in labor for 13½

^{*}For 8 patients it was impossible to obtain accurate definition of the duration of labor.

hours and was delivered under nitrous oxide-oxygen-ether anesthesia, $3\frac{1}{2}$ hours after the last dose of the analgetic. There was transverse impaction of the head with marked asynclitism. Autopsy was not performed.

Of the live infants 3 were premature, 3 were breech presentations, one had congenital heart disease, one, delivered of a mother with abruptio placentae, had severe cerebral anoxia, and one was extracted with great difficulty

because of impacted shoulders.

The average fetal heart rate was 138.3 before administration of the alphaprodine-levallorphan mixture, 137.4 at the end of the first stage of labor, and 150.4 immediately after delivery. Excessive bradycardia or tachycardia was not observed. All 201 live infants were discharged from the hospital in good health.

Table IV. Comparison of Average Duration of Labor in 192 Women Who Received Alphaprodine-Levallorphan, in a Control Series of 300 Patients Who Received Other Forms of Analgetic Medication, and in Series Reported by Other Workers

		AVERA	GE DURATION	OF LABOR I	N HOURS
		PRIM	MIPARAS	MUL	TIPARAS
SOURCE	ANALGETIC MEDICATION	HOURS	NO. OF PATIENTS	HOURS	NO. OF PATIENTS
Present series	Alphaprodine-levallor- phan	15.3	45*	8.2	147*
Control series	Miscellaneous	12.4	100	8.4	200
Eastman ¹⁹	Analgetic medication not given	18	Not given	12	Not given
Busby ²⁰	Analgetic medication not given	13.04	4,243	8.15	4,227
Carroll and Hudson ²¹		17.0	127	10.2	72
Carroll and Hudson	Promethazine and meperidine	12.8	135	9.2	165

^{*}For one primipara and seven multiparas it was impossible to obtain accurate definition of duration of labor.

Table V compares the average breathing times and crying times of 161 and 100 infants, born to mothers who had received, respectively, the alphaprodine-levallorphan mixture and other analgetic medication during labor and were all delivered under saddle block, and of 40 and 100 infants, born to mothers who had received these types of analgesia during labor and were all delivered with nitrous oxide-oxygen-ether anesthesia. The difference between these measurements in the saddle block groups is not statistically significant, but it is in the nitrous oxide-oxygen-ether groups. The high standard errors for the figures in the control group of patients delivered with nitrous oxide-oxygen-ether anesthesia indicate that there were marked differences between the individual values in this group.

Table V. Average Breathing Times and Crying Times of 201 Newborn Infants Whose Mothers Received Alphaprodine-Levallorphan Mixture and of a Control Series Whose Mothers Received Other Forms of Analgetic Medication

		TYPE OF A	NESTHESIA	
	SADDLE	BLOCK	NITROUS OXIDE	OXYGEN-ETHER
	ALPHAPRODINE- LEVALLORPHAN GROUP (161 INFANTS)	CONTROL GROUP (100 INFANTS)	ALPHAPRODINE- LEVALLORPHAN GROUP (40 INFANTS)	CONTROL GROUP (100 INFANTS)
Average breathing time (seconds)	4.5 ± 1.2*	7.4 ± 3.6	10.0 ± 2.1	50.5 ± 17.0
Average crying time (seconds)	8.5 ± 0.4	11.7 ± 3.8	17.8 ± 2.7	53.0 ± 16.8

^{*}Standard error.

Further analysis of these data disclosed that 27 of the 40 infants born to mothers who had received the alphaprodine-levallorphan mixture and were delivered under nitrous oxide-oxygen-ether, or 67.5 per cent, and 30 of the 100 babies born to mothers of the corresponding control group, or 30 per cent, breathed and cried within 10 seconds of delivery. The average breathing and crying times of the infants remaining in these two groups were 14.0 and 25.0 seconds in the alphaprodine-levallorphan group and 158.5 and 166.8 seconds in the control group. Three babies in the latter group did not breathe satisfactorily for 15, 17, and 18 minutes, respectively. In the alphaprodine-levallorphan group there were only 2 infants who did not breathe within 2 minutes. The mother of one had a premature separation of the placenta and the infant had signs of cerebral anoxia; the other baby was delivered with considerable difficulty due to impaction of the shoulders.

Table VI shows that the average "Apgar scores" of the infants in the two groups of the present series were slightly higher than those reported by Apgar¹⁸ in two similar groups.

Table VI. "Apgar Scoring" of 201 Newborn Infants Whose Mothers Received Alphaprodine-Levallorphan Compared With Scoring Reported by Apgar¹⁸

	AL	PHAP	RODIN	E-LEV	ALLORPHAN	SERIES	APGAR'S	SERIES
	NO. 0	F BAE			AVERAGE	NO. OF	AVERAGE	NO. OF
	10	9	4	0	SCORE	INFANTS	SCORE	INFANTS
Nitrous oxide-oxygen- ether group	20	18	1	1	9.2	40	8.2*	692
Saddle block group	119	41	1	0	9.7	161	8.9	25

*Cyclopropane-oxygen anesthesia.

The postpartum analgetic requirements of the patients in the alphaprodine-levallorphan series and of 164 women of the control series are presented in Table VII. If one compares the percentage of patients who did not require analgetic medication within 24 hours of delivery in the two groups in which nitrous oxide-oxygen-ether was used as anesthetic, it becomes obvious that there was less need for postpartum pain relief in the alphaprodine-levallorphan group than in the control group.

TABLE VII. POSTPARTUM ANALGETIC REQUIREMENTS OF 199 MOTHERS* WHO RECEIVED ALPHAPRODINE-LEVALLORPHAN DURING LABOR AND OF A CONTROL GROUP OF 164 MOTHERS WHO RECEIVED OTHER ANALGETIC MEDICATION DURING LABOR

TIME INTERVAL	ALPI	HAPRODINE SE	-LEVALLO	RPHAN		CONTRO	L SERIES	
(HOURS) BETWEEN DELIVERY AND FIRST DOSE ANALGETIC	1	TS WITH E BLOCK	NITROU	TS WITH US OXIDE- N-ETHER		TS WITH E BLOCK	NITROU	TS WITH US OXIDE- N-ETHER
MEDICATION	NO.	1 %	NO.	1 %	NO.	1 %	NO.	1 %
0- 2	3	1.9	3	7.5	5	5	2	3.1
2- 4	7	4.4	5	12.5	10	10	11	17.2
4-6	19	11.9	5	12.5	14	14	8	12.5
6-8	37	23.3	6	15.0	22	22	14	21.9
8-12	50	31.5	7	17.5	29	29	7	10.9
12-24	36	22.6	7	17.5	19	19	22	34.4
Patients not requir- ing analgetic medi- cation	7	4.4	7	17.5	1	1	0	0
Total	159	100.0	40	100.0	100	100	64	100.0

*One mother was excluded because she received analgetic medication which was in-advertently not recorded.

Retrograde partial amnesia for the period of labor was present in 25 of the 50 mothers interviewed.

Forty-four of the patients who had received the alphaprodine-levallorphan mixture, or 22 per cent, were nauseated or vomited within 24 hours after delivery. In half of these cases, emesis occurred more than once. In the control series the incidence of nausea and vomiting was 17 per cent, but only 1 per cent had more than one episode of emesis. In both series these figures do not include the episodes of nausea and vomiting during the first hour after delivery, since these are usually due to a variety of causes (e.g., pressure on the fundus, intravenous administration of Ergotrate, emergence from ether anesthesia, etc.).

The incidence of other postpartum complications, such as headache, backache, urinary retention, hemorrhage, etc., was about the same in both series.

Comment

Alphaprodine and levallorphan in a 50:1 ratio produced satisfactory analgesia in 200 parturients. A detailed study of the one stillbirth did not incriminate the analgetic medication. It was the opinion of the obstetrician that this death was due to obstetrical causes. Neither the 3 premature infants nor the twins delivered of a mother who had received 330 mg. of alphaprodine, 6.6 mg, of levallorphan, and 2.8 mg, of scopolamine during a labor which lasted 22½ hours showed any signs of respiratory or circulatory depression. In several instances parturients who were apprehensive after the administration of the saddle block were given a dose of the alphaprodine-levallorphan mixture 15 or 20 minutes prior to delivery without any depression of the newborn. These circumstances attest to the safety of the combined medication in the doses used. In fact, in several cases not included in the present series, initial doses corresponding to 1.25 to 1.33 mg, of alphaprodine per kilogram failed to produce respiratory depression of the parturients or the infants. The impression was gained on occasion, however, that these larger doses, in contrast to 1 mg. per kilogram doses, had a tendency to retard uterine contractions.

One multipara developed an incarcerated cervix after several hours of labor. After the patient had received a dose of the analgetic antagonist mixture corresponding to 1 mg. of alphaprodine per kilogram she fell asleep and two hours later was delivered vaginally of a normal baby, under saddle block anesthesia, without difficulties.

The alphaprodine-levallorphan mixture was readily accepted by the great majority of multiparas to whom other forms of analgesia had been administered during previous deliveries. There were only 10 mothers, or 5 per cent of the patients, who expressed disappointment about the fact that they were awake for most of the first stage of labor, although they had been promised by their obstetrician that they would not remember their labor or delivery.

The nursing staff in the labor rooms and delivery rooms preferred the alphaprodine-levallorphan mixture to other types of sedative-analystic medication because the parturients were free of pain, well sedated, and yet very cooperative. This was in contrast to the experience of the nursing staff with patients who had received large doses of barbiturates. Two of the nurses

who had been on duty in the labor rooms during the period of experimental use of the alphaprodine-levallorphan mixture requested to be given this medication when they were to have their babies.

It is of interest that the patients who had received the alphaprodine-levallorphan mixture and were delivered under saddle block did not complain of severe discomfort or pain when transabdominal pressure was applied to the fundus to facilitate the delivery of the head or the expulsion of the placenta. In contrast, most women in the corresponding group of the control series complained of severe discomfort when such pressure was exerted.

The ability of levallorphan to decrease average breathing times and crying times was not clearly evident in the infants born of mothers who had received saddle block anesthesia. When nitrous oxide-oxygen-ether was used, however, the breathing and crying times of the babies delivered of women who had been given the alphaprodine-levallorphan mixture were significantly shorter than the corresponding measurements in the control group. The greater safety of the alphaprodine-levallorphan mixture was particularly apparent when patients received nitrous oxide-oxygen-ether anesthesia for a longer period. Even in these instances the infants were never depressed for longer than 2 minutes, whereas with other forms of analgetic medication prolonged administration of nitrous oxide-oxygen-ether anesthesia resulted in respiratory depression of the newborn which occasionally lasted for 15 to 18 minutes.

Since it is known that narcotic antagonists do not counteract depression from inhalation anesthetics, the more favorable findings with the alphaprodine-levallorphan mixture are attributable to the action of the antagonist against narcotic-induced respiratory depression which is more accentuated with inhalation anesthesia than with saddle block anesthesia.

The results obtained with the alphaprodine-levallorphan mixture indicate that this combination has definite merits as an analgetic in obstetrics. The addition of the narcotic antagonist to alphaprodine renders the latter safer for mother and infant. Thus, this mixture can be administered until close to the time of delivery.

Fifteen parturients not included in the present series received 0.02 mg. of levallorphan per kilogram, followed after several minutes by 1 mg. of alphaprodine per kilogram in combination with 50 to 100 mg. of thiopental sodium. Additional fractional doses of alphaprodine were administered as needed in some cases. Nitrous oxide-oxygen was employed as anesthetic for delivery. These minimal doses of thiopental in combination with the analgetic and narcotic antagonist did not produce respiratory depression of either mothers or infants.

Alphaprodine and levallorphan in conjunction with succinylcholine was also used as supplement to nitrous oxide-oxygen anesthesia in 10 cases of cesarean section. Anesthesia was administered by the method described by Foldes and others, ¹² except that 5 minutes before delivery the mothers were given an additional 1 mg. of levallorphan intravenously; moreover, one minute before delivery they were hyperventilated with 100 per cent oxygen until the

umbilical cord was clamped. None of the babies delivered by this method showed any signs of narcotic-induced depression. These preliminary findings warrant the use of this technique in a larger series of cases of cesarean section.

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Summary and Conclusion

- 1. A premixed solution of alphaprodine (Nisentil) hydrochloride and levallorphan (Lorfan) tartrate, in a 50:1 ratio, was used subcutaneously for the production of analysis during labor in 200 patients.
- 2. The initial dose in terms of alphaprodine was 1 mg. per kilogram of prepregnancy weight. Four-tenths or 0.6 mg. of scopolamine was administered intramuscularly at the same time. One-half the initial dose of the alphaprodine-levallorphan mixture was repeated as required, with the second injection spaced at least 30 minutes after the first. Subsequent injections were administered at shorter intervals if needed. The total dose of the mixture, in terms of alphaprodine per patient, ranged from 48 to 330 mg.
- 3. Analgesia was excellent in 81.5 per cent of the parturients, good or fair in 13.5 per cent, and poor in 5 per cent.
- 4. Sixty-one per cent of the patients were awake, 35 per cent lightly asleep, and 4 per cent deeply asleep at the end of the first stage of labor. All patients were cooperative and relaxed.
- 5. The mode of anesthesia for delivery was saddle block in 159 and nitrous oxide-oxygen-ether in 40 women. (One patient was delivered without anesthesia.)
- 6. There were 198 single and 2 twin deliveries resulting in 201 live infants and one stillborn child. This death was attributed to obstetrical causes, not to the medication the mother received.
- 7. Respiratory or circulatory depression did not occur in mothers or infants, either during the antepartum or postpartum observations.
- 8. The duration of labor was not longer than with other forms of analgetic medication.
- 9. The average breathing times and crying times of the babies delivered under saddle block were not significantly shorter than of infants whose mothers were given the same type of anesthesia but who had received other analgetic medication during labor. However, when nitrous oxide-oxygenether was used for anesthesia, these measurements were significantly shorter in the babies of the present series than in infants of a corresponding control group.
- 10. The great majority of multiparas who had received other types of analgesia during previous deliveries, expressed preference for the alphaprodine-levallorphan mixture.
- 11. It is concluded that alphaprodine-levallorphan is an effective analgetic medication in obstetrics which is safe for both mother and infant and has advantages over other forms of analgesia.

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OBSTETRICAL ANESTHESIA*

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WHEN individuals undergo surgery it is generally agreed that it is not the anesthetic agent but rather it is the physician at the head of the table who makes for safe anesthesia. The same premise does not apply in obstetrical anesthesia because we are dealing with two patients, the mother and the unborn infant. Generally, the mother is young and healthy and will do well with any anesthetic agent or procedure. In contrast, the unborn child has a very delicate respiratory system. Most analgesics and anesthetics given to the mother are respiratory depressants. These substances readily pass the placental barrier and they have a profound effect upon the infant. It has been stated that up to 1.9 per cent of the infants are born with congenital anomalies incompatible with life.¹ Therefore, it is reasonable to assume that a mortality rate greater than this figure must in some portion be attributed to the ministrations of the obstetrician and anesthetist.

A few of the pertinent physiological principles must always be kept in mind and should merit review. As previously stated, all anesthetic drugs or agents given to a patient in labor, whether administered by inhalation or by the oral or parenteral routes, pass the placental barrier and have a depressing effect on the fetus. The effect may be great or small depending on the dosage, agent, and time of administration in relation to delivery. Fetal oxygen saturation is approximately 50 per cent.² If the newborn infant is a full-term, normal child and is born without undue trauma or drug depression, there will be a rapid upward adjustment of its blood oxygen saturation to normal adult levels. This adjustment to 95 per cent oxygen saturation of the blood will occur within fifteen minutes after delivery if no general anesthesia or analgesia is used and if the child is born by a normal spontaneous delivery at term. This does not mean that general anesthesia should not be used in obstetrics. It means that there is some risk involved and that the anesthetic should be properly chosen, timed, and administered so as to balance the added risk.

A second factor is oxygen transfer to the fetus which is dependent on a tension gradient toward the fetus. Eastman³ has calculated that the tension available to the umbilical vein blood in the placenta is 50 mm. of mercury or less. The maternal arterial oxygen tension is 90 mm. of mercury. This can

^{*}Presented at the annual meeting of the Royal College of Physicians and Surgeons of Canada, Toronto, Ont., Oct. 26 and 27, 1956.

be readily lowered: for example, the inhalation of pure nitrous oxide for half a minute will lower maternal oxygen tension to 50 mm. Nitrous oxide with adequate oxygen does not produce this effect. A third factor is the reserve of oxygen in combination with hemoglobin in the placenta, amounting to about 40 c.c. of oxygen. This constitutes a safety factor enabling the fetus to withstand temporary interruptions in the oxygen transfer. The safety factor is reduced by placental separation, placental disease and, possibly, prolonged labor. Another important factor is maintenance of maternal blood pressure. If maternal systolic pressure drops below 80 mm. of mercury it is possible that blood ceases to flow through the uterine muscle to the placenta. With these fundamentals in mind, we would like to describe anesthesia and analgesia as practiced at the Royal Victoria Hospital.

The practice of the principles of relaxation advocated by Read,⁵ or modifications thereof, has greatly reduced the amount of analgesia and anesthesia administered to the obstetrical patient. At the Royal Victoria Hospital, analgesia for the first stage of labor is used sparingly. The agents in common use are Seconal, Demerol, or hyoscine. During the second stage of labor three agents and techniques rate high, namely, Trilene (trichloroethylene), cyclopropane, and spinal anesthesia.

Trilene as an obstetrical anesthetic agent has been used in our institution almost since its introduction by Hewer.⁶ It has been found to be a very satisfactory agent, so that at the present time 50 per cent of the obstetrical administrations are with Trilene. It is used with an inhaler such as the Cyprane⁷ for self-administration by the patient in the latter part of the first stage of labor and with nitrous oxide and oxygen by the anesthetist for the second and third stages of labor. Some of the advantages of Trilene are that it provides excellent analgesia, it produces no troublesome secretions, and nausea or vomiting is rare; it has no effect on uterine contractions, and though it passes the placental barrier rapidly it has no effect on the baby; last, the mother retains her pharyngeal reflexes.

We are told that of the ten million anesthetics administered in the United States each year, three million are for obstetrical deliveries. The chief cause of death as a result of anesthesia in the obstetrical patient is aspiration of vomitus. With the use of Trilene, the patient retains her pharyngeal reflexes and the serious complication of aspiration of vomitus can be avoided. The complication of neurological palsies has not occurred in our institution because the anesthetists use special machines such as the Boyles or Walton which have no absorption apparatus. (These machines are of British manufacture. Soda lime or other substances used with Trilene for absorption of carbon dioxide cause a breakdown of Trilene into substances which are toxic to nerves.)

The other general anesthetic agent in common use is cyclopropane. It is favored because of its relative potency, rapidity of induction of anesthesia, the high concentration of oxygen available with its administration, and the low incidence of postpartum vomiting; even though the strength of uterine contractions is decreased, the tone of the uterine muscle is maintained. Cyclopropane definitely passes the placental barrier and may cause respiratory depression of the baby. Other objections generally raised with reference to the use of cyclopropane are explosibility and its tendency to produce cardiac arrhythmia. There has never been an explosion as a result of cyclopropane

anesthesia in our institution because all recommended precautions are observed. In addition, the early use of cyclopropane was pioneered by Dr. Harold Griffith⁹ of Montreal, and consequently the anesthetists in this area are particularly adept in its use.

Of the regional techniques, spinal anesthesia is our choice. Spinal anesthesia is preferred to caudal anesthesia because of its greater ease of establishment, the introduction of the agent in the clean area of the lumbar region rather than in the potentially infected sacral area. In addition, the required dose of local anesthetic agent is one twentieth of that needed for caudal anesthesia and caudal anesthesia may fail in 7.2 per cent of cases because of abnormalities in the bony structure of the sacrum. Apgar¹⁰ of the Presbyterian Hospital in New York gives her failures in caudal anesthesia as 10 per The advantages of the regional technique are the psychological effect on the mother, who remains awake during the delivery, and is able to see her baby immediately and to hear it cry. The preservation of the contractility of the uterus and, therefore, reduction in blood loss are most important; and last, but certainly not least, valuable protection is afforded the infant, who breathes and cries immediately on delivery because no depressant anesthetic agent has been given. In a three-year survey at the University of Washington the mortality rate of infants protected by conduction anesthesia was 100 per cent lower than that of the nonconduction group which included delivery without anesthesia.¹¹ The main objection raised to conduction techniques has been that these techniques increase the incidence of forceps deliveries.

TABLE I. THE NUMBER OF SPINAL ANESTHETICS ADMINISTERED IN THE FIVE YEARS REPORTED IN THIS SURVEY. TOTAL NUMBERS OF PRIVATE AND STAFF DELIVERIES WERE APPROXIMATELY EQUAL.

		SPIN	ALS
YEAR	DELIVERIES	PRIVATE	STAFF
1951	3,164	938	187
1952	3,398	968	157
1953	3,311	656	119
1954	3,415	618	122
1955	3,315	428	74
Total	16,603	3,608	659

In order to administer conduction anesthesia properly one must understand the innervation of the uterus and vagina. Cleland¹² in a series of investigations in animals established that the sensory fibers to the cervix and lower uterine segment are derived from the sacral and lower lumbar spinal nerves; those of the upper part of the fundus are from the upper lumbar and twelfth thoracic spinal segments. The motor innervation is not quite as clear but extends from the third thoracic to the second lumbar segments. We know that anesthesia above the eighth dorsal segment definitely reduces the force of uterine contractions.

Our agent of choice is Pontocaine 1 per cent weighted with glucose-saline 10 per cent. The dose is 5 to 10 mg., with the average being 7.5 mg. This is administered with the patient in the sitting posture, between contractions, and the patient is maintained sitting for five minutes. This technique limits the anesthesia to the eleventh or tenth dorsal segment, freeing the patient of pain but maintaining the contractility of the uterus.

The main objection that has been raised to the use of spinal anesthesia has been the danger of neurological complications. High liability insurance rates for anesthetists employing spinal techniques in some localities have made this form of anesthesia prohibitive. As physicians we should not allow insurance

companies to dictate to us how we shall practice medicine. At the Royal Victoria Hospital there have been no serious neurological complications in the obstetrical patients.

The less serious neurological complication, that of postspinal headache, is ever present. In our cases headaches occur in 5 to 10 per cent of cases. The postspinal headache is a manifestation of the reduction of cerebrospinal fluid pressure. This is not necessarily due to a leakage of cerebrospinal fluid from the site of the lumbar puncture. Several authors^{13, 14} have described the reduction in incidence of postspinal headaches, by using fine gauge lumbar puncture needles, as fine as number 27. We are still using a 20 gauge needle because we believe that the act of doing a lumbar puncture in some way lessens the effective secretion of the choroid plexus. Therefore, adequate hydration of the patient is the most important prophylactic measure in the prevention of postspinal headaches, as this provides a free store of fluids for the choroid plexus to draw upon. The sudden release of intra-abdominal pressure after delivery, resulting in a pooling of blood in the splanchnic area, may contribute to the higher incidence of postspinal headaches in the obstetrical patient. Treatment of the headaches when they develop again is hydration, either by mouth or by the intravenous route. If this fails we administer 5 per cent alcohol intravenously.

Very recently we have started to use some continuous epidural anesthesia. However, in our hands it is too early to report this as an established technique in obstetrical anesthesia.

TABLE II. UNCORRECTED MORTALITY RATE FOR THE FIVE-YEAR SURVEY 16,603 DELIVERIES

1951	2.3%	
1952	2.3% 2.2%	
1953	2.2%	
1954	2.2%	
1955	1.8%	

TABLE III. FETAL DEATHS IN 1955 TOTAL VIABLE BIRTHS 3,375

Postpartum and neonatal deaths	25	0.8%
Deadborn and stillborn	35	
All inclusive	61	1.8%

The advent of relaxant drugs has reduced the need for profound anesthesia, so that at the present time spinal anesthesia is reserved for the primiparous patient and for difficult deliveries. In Table II fetal mortality was reduced to 1.8 per cent in 1955, of which 1 per cent was deadborn or stillborn.

Anesthesia for cesarean section must receive special consideration. Since 1942 we have been using a spinal technique developed by our anesthesia department and reported in a paper written by Dr. A. Torrie. Spinal anesthesia is our technique of choice, unless there are contraindications. The patient receives no premedication other than atropine or hyoscine. These patients are prone to have a drop in blood pressure; consequently all precautions are taken to avoid this condition. The patient receives ephedrine, another grain, fifteen minutes before the spinal anesthetic is administered, another grain is given at the site of the lumbar puncture, which is performed with the patient in the sitting position. Pontocaine-glucose, 15 mg., is the standard dose of anesthetic agent. The patient is then returned to the supine position and is not lifted,

TABLE IV. FIVE-YEAR SURVEY OF TYPE OF ANESTHESIA ADMINISTERED TO PATIENTS FOR CESAREAN SECTION, INCLUDING FETAL MORTALITY

YEAR	GENERAL	LOCAL	SPINAL	FETAL MORT	ALITY
1951	3	0	134	7	
1952	2	0	124	7	
1953	2	1	98	6	
1954	9	3	133	3	
1955	7	0	121	5	
Total	23	4	610	28	(4.5%

Table V. Anesthetic Agents Administered for Cesarean Section in 1940-41: A Comparative Study
Total Deliveries: 4,654

Cesarean sections Anesthetic	169	3.8%
General	71	
Local	82	
Spinal	16	
Maternal deaths	3	
Infant deaths	9	5.4%

TABLE VI. INDICATIONS FOR CESAREAN SECTION FOR THE 28 FETAL DEATHS IN THE FIVE-YEAR SURVEY. ASTERISKS INDICATE PATIENTS WHO HAD GENERAL ANESTHESIA; ALL OTHERS HAD SPINAL ANESTHESIA

Bony disproportion and repeat cesarean section	7	
Inertia	3	
Rh isoimmunization	6	
Eclampsia	1	
Abruptio placentae	4**	
Placenta previa	4*	
Fibroids	2	
Diabetes	1	
Total	28	

Table VII. Clinical Classification of Fetal Deaths in 637 Cesarean Sections, 1951-1955

Died before operation	6	
Nonviable (under 1,000 grams)	2	
Stillborn	3	
Died post partum (up to 30 days)	17	
 Total	28 (4.5%)	
Maternal deaths	0	

TABLE VIII. PATHOLOGICAL DIAGNOSIS AT AUTOPSY OF CAUSES OF FETAL DEATHS. ASTERISK DENOTES NONVIABLE FETUSES THAT WEIGHED LESS THAN 1,000 GRAMS

Macerated	6*	
Congenital anomalies	. 2	
Nonviable	2	
Atelectasis		
Premature	7*	
Full Term	2	
Prematurity	2*	
Hemolytic disease	6	
Intracranial hemorrhage	1	
Total	28	

shifted, or placed in stirrups. Oxygen is administered until the baby is delivered. At this time morphine or Demerol is administered intravenously and no further supplementation of anesthesia is required. The results for both mother and child have been very satisfactory.

Tables IV through VIII present an analysis of our results in the cesarean section patients. In the years from 1951 to 1955, most cesarean sections were completed under spinal anesthesia. There were 28 fetal deaths, a percentage of 4.5, and we had no maternal deaths. The years 1940-41 were taken for comparison. These years were chosen because this was the change-over period from general and local to spinal anesthesia. At that time the fetal mortality rate was 5.4 per cent and there were 3 maternal deaths.

In conclusion, this presentation has outlined the common anesthetics and techniques as used at the Royal Victoria Hospital on the obstetrical service. It must be emphasized that the complete individualization in selection of agents, dosage, and routes of administration under the able guidance of a trained team points toward the true path to safety. In the United States and Canada, anesthesia rates third among the causes of maternal mortality and this is certainly worthy of serious consideration. Above all one must remember that the newborn infant needs oxygen and that the anesthetist is the one who can give the fetus this necessary substance through the mother's circulation. Every cog in the wheel is important in making that newborn a bouncing, pink, and lusty infant, rather than the cyanotic, limp infant who some day may be spastic, convulsive, or mentally deficient.

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PROTECTION BY PREGNANCY AGAINST THE DEVELOPMENT OF EXPERIMENTAL ARTERIOSCLEROSIS AND METASTATIC CALCIFICATION*

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THE possible influence of pregnancy and of sex hormones upon the development of clinical or experimental cardiovascular diseases has been the subject of numerous investigations, but the relevant data are rather difficult to interpret.¹⁻⁷ One of the most serious handicaps in research on the influence of pregnancy upon the pathogenesis of arteriosclerosis was the lack of a suitable test object for controlled laboratory investigations. In most of the laboratory animals, pregnancy is too short to influence the development of the common chronic types of experimental arteriosclerosis, and the procedures used for the production of acute arterial lesions tend to induce abortion. It seemed of special interest, for the analysis of these interrelations, to devise a technique which does not interfere with the progress of gestation but permits the consistent production of pronounced arteriosclerotic changes within a few days in the common laboratory rat.

It is the object of this communication to report upon experiments in which this has been accomplished. They show that heavy overdosage with AT-10 (dihydrotachysterol) invariably induces marked arteriosclerotic lesions of the Mönckeberg-sclerosis type within 6 to 9 days in nonpregnant, but not in pregnant rats.

Materials and Techniques

For all our experiments, adult female albino rats of the Wistar strain were used; the controls exhibited normal sexual cycles, while the experimental animals were 7 to 9 days pregnant at the beginning of the treatment. AT-10 (Hytakerol†) was administered daily by gavage, in 0.4 ml. of sesame oil, with the use of a thin rubber catheter. Throughout the experiment the animals were fed exclusively on Purina Fox Chow and Pablum. At autopsy the degree of arteriosclerosis was easily assessed, in terms of an arbitrary scale of 0 to 3, by mere macroscopic inspection of the calcified plaques in the aorta and its main branches. In advanced cases these vessels were transformed into rigid, brittle, calcified tubes. Metastatic calcification in other organs was gauged similarly. Immediately after autopsy, specimens of the organs were fixed in neutral formalin (for the subsequent histochemical demonstration of calcium with the aid of the von Kóssa stain) and in Susa solution (for the study of PAS-positive material with the Hotchkiss-McManus technique).

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 $^{^{*}}$ This work was supported by a grant from the Irwin Strassburger Memorial Medical Foundation.

Results

A first orientating experiment was performed on 6 pregnant and 6 non-pregnant rats. Both groups had a mean initial body weight of 214 grams (range: 163 to 293 grams) and were given 500 mcg. of AT-10 daily for six days. By the end of this period one of the nonpregnant rats died, while the survivors were all obviously moribund and greatly emaciated; on the other hand the pregnant animals were still in relatively good condition. Autopsy on the last day of treatment showed pronounced calcification of the aorta, heart, and kidneys in all the nonpregnant rats, while 2 of the pregnant animals showed no sign of vascular lesion or of ectopic calcification, and the remaining 4 exhibited only slight morbid changes of this type. It was concluded that, although pregnancy probably has some protective effect upon the syndrome of AT-10 intoxication, we had used too high a dose of the drug to demonstrate this with sufficient clarity.

Consequently, in the principal experiment, the daily amount of AT-10 was diminished to 250 mcg. This dose was given during the first nine days of observation and then the animals were allowed five days of recovery, autopsy being performed on the fourteenth day. In this final experiment we used three types of controls, to check the possible influence of several unavoidable variables, such as the stress of the gavage itself and the fact that pregnant animals are, of necessity, heavier than controls of the same age. Group 1, consisting of 10 nonpregnant rats with the same initial body weight as the 10 pregnant rats of Group 4, received only 0.4 ml. of the sesame oil vehicle by daily gavage. The rats of Groups 2, 3, and 4 were given daily gavages of AT-10 in 0.4 ml. of sesame oil. The 10 rats of Group 2 were of the same age, while the 10 rats of Group 3 had essentially the same initial body weight as the pregnant rats in Group 4. The mean initial and final body weights (with their standard errors) as well as the principal autopsy findings are summarized in Table I.

TABLE I. PREVENTION BY PREGNANCY OF ORGAN CHANGES NORMALLY PRODUCED BY AT-10

							CA	ALCIFICATIO	N	
GROUP	INITIAL BODY WEIGHT (GRAMS)	FINAL BODY WEIGHT (GRAMS)	GAIN	STATUS	TREAT-	HEART	AORTA	KIDNEYS	STOM- ACH	TAL MUS- CLES
				Not						
1	237±1.8	242±4.3	+2	preg- nant Not	Oil	0	0	0	0	0
2	204±2.0	134±2.9	-34	preg- nant Not	AT-10	++	+++	++	+++	+
3	219±3.9	156±3.3	-29	preg- nant	AT-10	++	+++	++	++	+
4	226±5.6	182±14.9	-19	Pregnant	AT-10	0	(One rat +)	(One rat ++)	0	0

It will be noted that, with the exception of slight calcification of the aorta and moderate calcium depositions in the kidney of one rat, none of the AT-10 treated pregnant animals (Group 4) showed any morbid changes at autopsy, while all the AT-10 treated nonpregnant rats exhibited severe arteriosclerosis and ectopic calcium depositions in various organs. It is also noteworthy that the pregnant AT-10 treated animals suffered only a slight

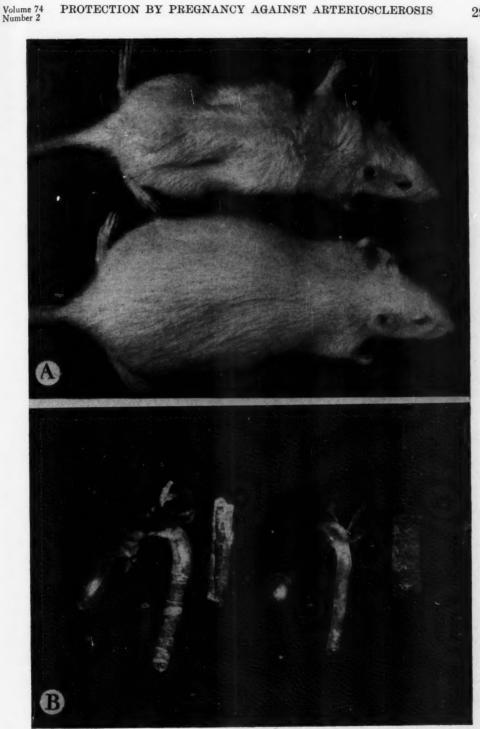


Fig. 1.—A, Appearance, after AT-10 treatment, of both a nonpregnant rat (top) and one which was pregnant during the experiment but is shown here after delivery. Note considerable emaciation and shaggy fur of the top rat in comparison with the normal appearance of the animal protected against AT-10 by pregnancy. B, Heart and thoracic aorta, with a separate opened piece of the abdominal aorta of a nonpregnant rat (left) and one which was pregnant during the experiment. Both animals received AT-10. Note white calcified spots in the heart and "gooseneck" appearance of the thoracic aorta due to intensely calcified cross bands. The portion of the abdominal aorta (incised lengthwise) is so stiff that its edges do not open. In comparison, the heart and aorta of the animal protected by pregnancy retain their normal appearance. The opened piece of abdominal aorta is so supple that it flattens out, and so transparent that the background pattern shines through its wall.

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loss in body weight (mainly due to delivery) and were obviously in perfect health, while all the nonpregnant AT-10 treated rats exhibited severe emaciation and were virtually moribund.

Fig. 1 illustrates the intensity of the emaciation and of the arteriosclerosis of the aorta as seen at autopsy in a typical animal of Group 2, in comparison with the normal appearance of the aorta of a similarly treated pregnant rat of Group 4.

Histologic examination of the aorta revealed the typical features of the so-called Mönckeberg sclerosis with the deposition of regular, calcified layers within the vessel wall (Fig. 2). Occasionally, there were exulcerations of the intima, with the formation of thrombi upon the denuded surfaces.

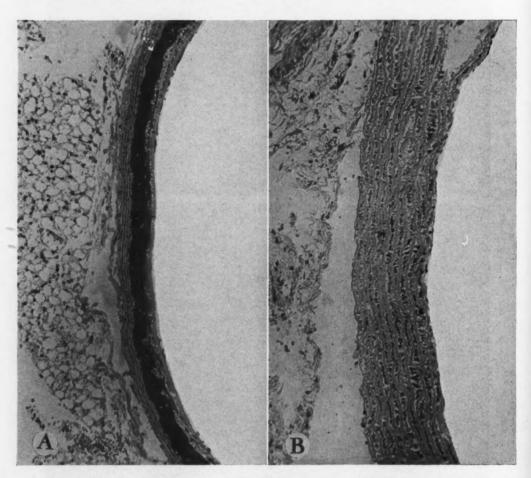


Fig. 2.—Microscopic sections of a nonpregnant (A) and a pregnant (B) rat, both treated with AT-10. Only in the nonpregnant rat did the compound produce calcified bands characteristic of Mönckeberg sclerosis. (von Kóssa calcium stain.)

It may be mentioned incidentally that none of the pregnant rats had abortions during the period of AT-10 treatment, but 9 of them were delivered before termination of the experiment, and one was still pregnant on the day of autopsy. In this experimental series, however—presumably because the animals were pregnant throughout the period of treatment—morbid changes due to AT-10 were effectively prevented by gestation in all cases.

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Comment

Our observations clearly indicate that the state of pregnancy offers protection against the production, by AT-10, not only of arteriosclerosis, but also of soft-tissue calcification and excessive catabolism.

The fact that overdosage with steroids of the vitamin D group can produce Mönckeberg sclerosis-like changes in the arterial system and metastatic calcification in the heart, kidneys, stomach, and skeletal muscles of the rat was established long before the discovery of AT-10,8,9 by the use of impure ultra-violet-irradiated ergosterol preparations. It was also noted that, in man, the development of a parathyroid adenoma can induce similar organ lesions. Since AT-10 is a member of the vitamin D group and exerts pharmacologic actions which resemble those of the parathyroid hormone, it is highly probable that these substances act through similar mechanisms.

It remains to be seen, however, whether there is any relationship between clinical arteriosclerosis and the morbid changes which we induced experimentally. The mechanism through which pregnancy offers protection is likewise still unknown. The calcium avidity of the embryonic tissues may play a role, but actually we found no abnormal calcification in the young delivered by the rats which had received AT-10 during pragnancy. It is also possible that embryonic or placental tissue detoxifies AT-10 through the agency of some local chemical mechanism, or that the hormones produced by the maternal endocrine glands and placenta are responsible for the protection. In any event, the experimental arrangement described in this communication offers a simple technique which can assist us in the analysis of this singular phenomenon.

In general, pregnancy tends to sensitize experimental animals to the toxic effects of various drugs. This has been shown, among other compounds, for amyl nitrate, 11 tyrosine, 12 and di-isoproplyfluorophosphate. 13 There are also many substances to which pregnant and nonpregnant animals are about equally sensitive. 14 Since AT-10 is particularly toxic to the cardiovascular system, it is relevant that the rise in blood pressure normally produced by partial constriction of the renal artery is diminished, while that caused by desoxycorticosterone overdosage is not significantly influenced by gestation. 15 On the other hand, it is well known that certain connective tissue diseases, for example, rheumatoid arthritis, are often beneficially influenced by gestation in women. It is hoped that, by the use of AT-10 intoxication as an indicator, it will be possible to learn more about the mechanism through which pregnancy can afford protection, particularly against agents which tend to cause damage in mesenchymal tissues.

Summary

Experiments on Wistar albino rats show that doses of AT-10 (dihydrotachysterol), which in nonpregnant animals produce severe arteriosclerosis with calcium deposition in various soft tissues and a pronounced loss in body weight, are well tolerated during pregnancy.

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CARBOHYDRATE METABOLISM IN PREGNANCY*

Hepatic Glycogen Synthesis in the Rat

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LTHOUGH there is a voluminous literature concerning hepatic glycogen A synthesis and breakdown under various physiological conditions, few direct observations have been made that relate to glycogen formation and storage in pregnancy. For many years it has been assumed that hepatic glycopenia was characteristic of gestation, an impression stemming from Hofbauer's11 concept of the Schwangerschaftsleber characterized morphologically by fatty infiltration and loss of glycogen. German clinicians attributed the "ketosis" of pregnancy described by Bokelmann, 2, 3 by Schmidt, 19 and others 13, 17, 18 to altered liver function and a disturbance in hepatic lipid metabolism believed to be intimately related to this glycopenia. Although a lowered threshold to ketosis¹⁰ or physiological ketonemia of pregnancy¹⁶ is questionable, the concept of hepatic glycopenia has persisted in clinical thinking. Supporting evidence for this is fragmentary. The much-quoted study of Schmidt and his co-workers¹⁹ indicated, however, that hepatic glycogen was significantly decreased in the pregnant dog. More recently, Campbell and Kosterlitz⁶ have reviewed the biochemical changes in the liver during pregnancy and report that hepatic glycogen is decreased in the pregnant rat. Histochemical studies of liver biopsies in normal human pregnancy fail to substantiate the historical viewof Hofbauer that significant morphological changes occur in the liver during pregnancy, and evidence of glycogen deficiency was not observed. ¹² Although the factors affecting hepatic glycogen deposition have been considered in detail in Swensson's²¹ monograph, the effect of gestation is not considered.

Earlier studies in this laboratory⁵ were consistent in showing decreased plasma inorganic phosphorus depression following a glucose load during gestation. One possible interpretation of this observation was suggested by Forsham and Thorne⁸ who observed similar flattening or attenuation of the inorganic phosphate curves under conditions of starvation when the liver was believed to be deficient in glycogen. In this circumstance glucose was considered as "diverted" to the liver for glycogen synthesis instead of being utilized in the periphery with attendant decrease in inorganic phosphate

^{*}This investigation was supported in part by fund supplied by the Heart Association of Winston-Salem and Forsyth County, N. C., and by a grant-in-aid from Parke, Davis & Company, Detroit, Mich.

uptake. The experimental evidence implicating the peripheral tissues as the site of phosphate uptake with glucose loading has been reviewed by Kritzer and associates, 14 who offer indirect evidence in support of Thorne's view.

In view of the foregoing considerations, the present investigation was undertaken to obtain data pertaining to the effect of pregnancy on glycogen synthesis and storage.

Experimental Data

Female Wistar strain animals weighing 200 to 250 grams were employed throughout the study. Pregnant animals were sacrificed on the seventeenth day of gestation. Prior to experiment all animals were provided, ad libitum, with Rockland Rat Diet.* After fasting 24 hours, experimental animals were given a total of 2 mg. glucose per gram of body weight as a 5 per cent aqueous solution by intraperitoneal injection. The glucose was administered in two hourly doses over a 2 hour period. Two hours after the second injection animals were sacrificed by decapitation. The peritoneal cavity was rapidly opened and three aliquots of liver weighing approximately 0.3 grams each were removed and immediately placed in weighed tubes charged with 30 per cent potassium hydroxide. After they were reweighed, glycogen was isolated by the technique of Good and co-workers and glucose was estimated by the colorimetric method of Somogyi²⁰ as modified by Nelson.¹⁵ Instead of glucose control animals received a total dose of 0.04 ml. 0.9 per cent sodium chloride solution per gram of body weight in divided doses over a 2 hour period. The timing of injections, technique of administration, sacrifice, and preparation of liver aliquots were identical for control and experimental groups.

Liver glycogen was expressed as milligrams of glucose per gram of liver and as percentage of wet weight. The significance of mean values for experimental and control animals was assessed by Fisher's "t" test.

TABLE I. MEAN GLYCOGEN VALUES FOR EACH GROUP OF ANIMALS STUDIED

		MEA	N LIVER GLYCO	GEN
	NUMBER OF ANIMALS	MG. PER GRAM WET WEIGHT	σ	PER CENT WET WEIGHT
No Load (Saline).	_		1	
Nonpregnant	22	1.8	± 0.9	0.2
Pregnant	21	5.3	± 1.9	0.5
Glucose, 2 Mg. per	Gram			
Nonpregnant	27	16.4	± 3.5	1.6
Pregnant	37	20.5	± 4.2	2.1

In Table I are given the mean glycogen values for each group of animals studied. Attention is directed to the mean fasting values for pregnant (5.3 mg. per gram \pm 1.9) and nonpregnant (1.8 mg. per gram \pm 0.9) control animals. Statistical analysis of these data indicates that with the variance observed the difference between the means is highly significant (P = <0.001).

^{*}This preparation has the following composition: protein 24.8 per cent; fat 4.7 per cent; carbohydrate 49.3 per cent.

In separate experiments comparable values and variance were obtained for fasted animals not injected with saline. In Fig. 1, A the control data are plotted.

The liver glycogen concentration following glucose administration of the experimental pregnant and nonpregnant animals is also shown in Table I and Fig. 1, B. The difference of 4.1 mg. per gram between the mean values obtained appears not to be significant when appropriate correction is allowed for the mean fasting control values for each group. Thus, the mean increment in glycogen synthesized becomes 14.6 mg. per gram for nonpregnant and 15.2 mg. per gram for pregnant animals (Fig. 1, C). When Fisher's "t" test is applied to these data no significance can be demonstrated.

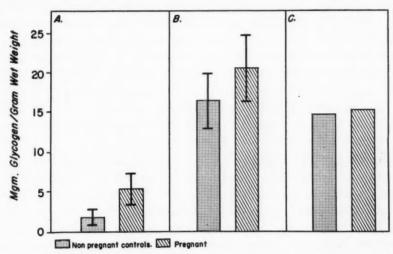


Fig. 1.—A, Fasting values for pregnant and nonpregnant control animals receiving saline alone. B, Increments in glycogen, expressed as glucose, in control and pregnant animals. C, Increments in glycogen in nonpregnant and pregnant animals after glucose administration corrected for the fasting glycogen levels shown in A.

The vertical lines in the nomographs represent ± one standard deviation from the mean.

Comment

The data presented indicate that the liver of pregnant rats is neither deficient in glycogen nor defective in glycogen synthetic activity with glucose as precursor. Within the limits of error inherent in our techniques the values obtained are considered valid. For nonpregnant animals the figures for glycogen content of liver reported are comparable to those of Cori, Barbour, and Swensson. The latter author has reviewed in detail the factors influencing liver glycogen deposition in laboratory animals. Significant diurnal variations in glycogen content are characteristic of the rat, and the literature is consistent in showing glycogen depletion with fasting followed by small increments after 24 hours. The experimental plan employed appears to have controlled any such variables. Close correspondence of our triplicate analyses of liver samples is in agreement with Swensson's observation of uniformity of glycogen distribution in the rat liver.

The contradictory report of Campbell and Kosterlitz⁶ describing hepatic glycopenia in the pregnant rat is difficult to interpret. It is possible that the

hooded rats studied may behave differently from Wistar animals regarding glycogen storage. Their observations were not made on fasted animals, however, and the glycogen values are referred to the desoxyribose nucleic acid content of the liver which these authors report to be significantly increased by pregnancy. Accordingly, the glycogen loss reported for pregnant animals may be a relative rather than absolute one on the basis of conventional wet weight notation.

As noted, our data fail to demonstrate hepatic glycopenia in the pregnant rat. Moreover, although the absolute values are small, the maternal rat liver characteristically has greater stores of glycogen than livers of control animals under identical experimental conditions and the ability to synthesis glycogen from glucose appears to be unaltered by gestation when allowance is made for initial fasting levels. These data are consistent with those of Ingerslev and Teilum¹² for human liver biopsy material in which no decrease in glycogen was demonstrated by histochemical methods. Our animal observations are also consistent with unpublished data from this laboratory indicating that glycogen storage and mobilization are unaffected in human pregnancy on the basis of comparable hyperglycemic responses to glucagon (hyperglycemic-glycogenolytic factor) in pregnant and nonpregnant human subjects.

An interesting item for speculation is the small but significant increase in fasting glycogen content of the maternal livers. It is possible that this is accountable by differences in physical activity or dietary intake prior to experiment. Another possibility is that alterations in hepatic phosphorylation reactions occur in the direction of glycogen conservation. Although the influence of female sex hormones on carbohydrate metabolism is to a large degree uncertain, Wade and Jones²² have shown that progesterone accelerates hydrolysis of liver adenosine triphosphatase, and estrogen may affect the hexokinase reaction in certain tissues.⁴ In this connection, Walaas²³ has reviewed the effect of estrogens on rat liver glycogen and has shown that prolonged estrogen administration is productive of significant increases in the hepatic glycogen content of spayed animals.

Finally, the present observations and our glucagon data do not support the view that attenuation of plasma inorganic phosphate response to glucose loading is attributable to glucose diversion to the glycogen-depleted liver in pregnancy. The interpretation of flat phosphate curves by Forsham and Thorne may be tenable under conditions of starvation with true hepatic glycopenia, a circumstance considered unlikely in normal pregnancy on the basis of our data. It seems more likely that our phosphate data reflect changes in rates of peripheral utilization of glucose although at the present time the actual partition of phosphate is poorly understood.

Summary

1. Adequate stores of glycogen are present in the maternal rat liver. The values obtained under the experimental conditions outlined were slightly but significantly greater than nonpregnancy control values.

2. In the rat no evidence of alteration in glycogen synthesis from glucose was observed during pregnancy.

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THE THYROID IN PREGNANCY

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THERE is no unanimity of opinion as to what happens to the thyroid gland during pregnancy. Most opinions are based upon theoretical considerations and not upon the actual study of thyroid glands in pregnancy. Only four papers^{10, 12, 13, 16} on the histology of human thyroids during pregnancy, and no photomicrographs, could be found in the world literature (Table I).

TABLE I. LITERATURE FROM 1912 UNTIL 1951 ON HISTOLOGY OF THYROID GLAND DURING PREGNANCY

AUTHOR	LOCALITY	YEAR	NO. CASES	HISTOLOGIC FINDINGS
Engelhorn ¹⁰	Erlangen, South- west Germany	1912	6	Colloid-rich gland with hyper- trophy. Macrofollicular
Knaus ¹³	Graz, Austria	1924	4	Colloid-rich glands. No hyper- trophy of epithelium
Hiilesma ¹²	Helsinski, Finland	1948	8	Four colloid rich, epithelial hyper- trophy. Four colloid poor, me- dium-small follicles, cuboid or columnar epithelium
Leicher ¹⁶	Solingen, West Germany	1951	10	Two marked epithelial hyperplasia. Eight had follicles above 320 μ
Total cases			28	22 colloid rich. 24 hypertrophic epithelium

Material and Methods

We had the opportunity of studying histologically an unusually large number of thyroids and goiters from pregnant women. Sixty-five thyroids were obtained by autopsy. One of us (C. A. H.) had the privilege of studying the microscopic slides of thyroids from autopsies of 35 pregnant women in the Armed Forces Institute of Pathology, Washington, D. C.* Forty-seven thyroids from nonpregnant women of the same age group served as controls. Twenty-seven patients with goiters in pregnancy were operated upon in the Hertzler Clinic during the last 25 years.

After gross description, the formalin-fixed tissue was embedded in paraffin. The 8 μ thick sections were stained with hematoxylin and eosin, some with Mallory's aniline blue stain. The size of the follicles and height of epithelium were measured in each gland with the micrometer eyepiece. Gross and histologic data were entered in a chart together with the clinical findings.

^{*}We are very grateful to Capt. Silliphant, Director of the A.F.I.P., and to Dr. G. A. Klinck, Chief of Endocrinological Pathology, for the courtesy and helpfulness extended.

Pregnancy Thyroids (Autopsy)

Age and Localities.—The ages of the 65 women autopsied varied between 14 and 40 years; 5 women were less than 20 years old, 24 were in the third decade, and 26 in the fourth decade. Sixty of the women were white, one was Negro, one part Indian from Mexico. Fourteen of our patients were from Ohio, 3 from Kansas, 5 from Oklahoma, and one each from Chicago and Brooklyn. The cases from the Armed Forces Institute of Pathology files were from the following localities: one each from Colorado, North Carolina, New York, Georgia, Kentucky, Maryland, Washington D. C., 2 from South Carolina, 2 from Washington, 7 from California, 9 from Texas, 4 from overseas, 1 from Germany, 1 from Austria, and 2 from Japan.

Duration of Pregnancy.—In 7 cases, the month of pregnancy was not given. Fourteen thyroids were from women who had died shortly after delivery; 9 glands were obtained during the first trimester, 14 between the fourth and sixth months of pregnancy, and 21 in the last trimester (Table II).

TABLE II. DURATION OF PREGNANCY AT TIME OF DEATH

TR	IMESTE	RS	LESS THAN 2 WEEKS	TWO TO FOUR WEEKS	
1	2	3	AFTER DELIVERY	AFTER DELIVERY	UNKNOWN
9	14	21	12	2	7

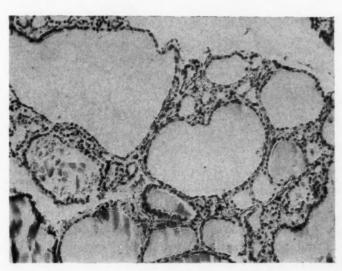


Fig. 1.—Thyroid gland of 33-year-old woman from Ohio one day after cesarean section. Cause of death was eclampsia. The thyroid was enlarged and had no nodules. The average follicle size was 250 μ . In the large follicle there is a flat cushionlike elevation of the wall with epithelium about 9 μ in height.

Weight of Thyroid.—The weight of the autopsy thyroids varied between 4 and 200 grams; 10 weighed less than 20 grams, 38 between 20 and 30 grams, and 5 weighed above 35 grams, which has been accepted as the upper limit of nongoitrous glands by pathologists of this country.

Nodules.—Only 4 thyroids, one from West Germany and three from Ohio, had nodes on gross inspection. In one gland from Ohio a minute non-encapsulated sclerosing adenocarcinoma was found by microscopic examination.

Average Diameter of Follicles.—The majority of thyroids showed large follicles with abundant and well-stained colloid. Vacuoles in the colloid were

frequently seen. In 56 of the 65 glands the average diameter of the follicles varied from 200 to 400 μ , 30 glands had an average diameter exceeding 300 μ , and 6 had average diameters of from 400 to 600 μ . (Figs. 1 and 3). Only in 3 glands were the diameters of the follicles less than 200 μ . The diameter of follicles in normal thyroids from 47 nonpregnant young women varied between 100 and 430 μ , with an average of 287 μ .

Height of Follicle Wall.—In spite of the large size of the follicles and the abundance of colloid, the epithelium was not flat, its height varied in the thyroids from 2.9 to 14.9 μ . In 5 glands the height of the epithelium did not exceed 6 μ . In 46 glands it measured 8 μ and more. Four glands had an epithelial height exceeding 11 μ . In the 47 normal thyroid glands from nonpregnant women, the height of the follicle epithelium varied from 2.9 to 8.7 μ . In 8 glands it measured 8 to 8.7 μ , while in 30 it did not exceed 6 μ .

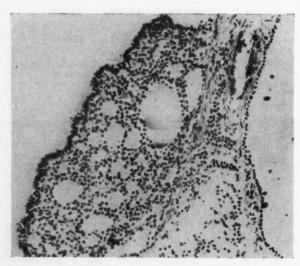


Fig. 2.—Sanderson's proliferative area in follicle wall of thyroid from West Germany. Twenty-one-year-old woman, uremia following artificial abortion in third month of pregnancy. The thyroid weighed 21 grams and the average diameter of follicles was 450 μ .

Segments of hypertrophic epithelium were present in the follicle wall of 54 glands, and absent in 11. Hyperplastic elevations of the wall with columnar epithelium and new formation of small acini were seen in 14 of the 65 autopsy thyroids.

Comment.

The increase in weight of the thyroids, if present at all, was not significant during pregnancy. The slight enlargement noticed so often clinically is probably due to hyperemia of the gland. Also the presence of nodules was not increased in our material. Noteworthy, however, were the microscopic characteristics of the pregnancy thyroids. Our findings confirm the view of earlier investigators^{10, 12, 14, 16} that during pregnancy the thyroid has large follicles with abundant colloid.

Forty-five of the 65 glands, almost three-fourths of our cases, had an average follicle diameter above 250 μ , only 20 had diameters between 130 and 250 μ . The colloid was thin or medium thick, and marginal vacuoles, which are regarded as a sign of colloid resorption, were frequently seen. That these wide follicles with abundant colloid were not due to stagnation of colloid or

"involution" of the thyroid was evident from the height of the follicle epithelium. In many follicles one or more segments of columnar and high cuboid cells were found in an otherwise low follicle wall. On these hypertrophic segments the presence of colloid vacuoles indicated active colloid resorption.

In 46 of the 65 pregnancy glands (75 per cent), epithelial cells measured above 8 μ , and 8 had cells above 11 μ . This incidence contrasts with the thyroids from nonpregnant individuals of the same age range, where only 13 (28 per cent) had cells of such height. Sanderson's cushionlike proliferations are generally regarded as evidence of a goitrogenic factor. In Kanass we observed a 15.8 per cent incidence in nonpregnant individuals. The percentage in our 65 pregnancy thyroids was 27.5 per cent, which would support the view that during pregnancy the thyroid shows increased activity (Fig. 2).

Recent experiments by Welch,²¹ in our laboratory, suggest that increased secretion of progesterone acts as a mild goitrogenic agent during pregnancy.

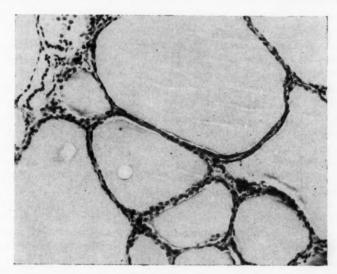


Fig. 3.—Pregnancy thyroid from Oklahoma. The patient was 34 years old, in last trimester. The weight of the gland was 21 grams and the average diameter of the follicles was 315 μ . The epithelium varied from 2.9 to 11.6 μ .

Pregnancy Goiters (Surgical)

During 25 years, 27 pregnant patients underwent thyroidectomy in the Hertzler Clinic. During these years, there were 8,092 goiter operations and 1,228 deliveries. Therefore 0.3 per cent of the surgical goiter cases were in pregnant women, and 2.1 per cent of the pregnant women had to have goiter operations. Most of our patients (16) were multigravidas, while 11 patients (5 with diffuse and 6 with negligibles) underwent thyroidectomy during their first pregnancy. A fetal adenoma in a 41-year-old patient was removed during her seventh pregnancy. One patient was in her sixth and 2 in their fifth pregnancies at the time of operation.

Enlargement of the neck was present from 4 weeks to 20 years prior to admission. In most cases (23) enlargement of the neck antedated the current pregnancy, and in only one-sixth of the cases did the onset of goiter occur during pregnancy.

Thyrotoxic Symptoms.—In 6 of our 27 patients the clinical diagnosis was nontoxic nodular goiter. Twenty-one cases were regarded as toxic; of those,

12 were diagnosed as diffuse goiter and 9 as nodular toxic goiter. Nervousness, tachycardia with palpitation, and weight loss were the three most constant symptoms. This triad was present in 16 of the 21 toxic patients. The average weight loss of these 16 patients was 20.2 pounds. The average duration of hyperthyroidism on admission was 12 months. True exophthalmos occurred in 6 patients, and neck enlargement was present in every case. Only one patient had auricular fibrillation; she was 41 years old and had a colloid adenoma.

All our toxic patients had symptoms before the current pregnancy. In most instances the symptoms became more severe during pregnancy. In no case could an improvement of the toxic symptoms due to pregnancy be demonstrated. Only two patients suffered from severe vomiting, one had a colloid adenoma and the other an exophthalmic goiter. The average basal metabolic rate on admittance was above 28 per cent in exophthalmic goiter, 26 per cent in diffuse colloid goiter, and 45 per cent in follicular toxic adenoma.

Treatment.—In 12 toxic cases, preoperative preparation included administration of Lugol's solution. The patients with exophthalmic goiter (3), diffuse colloid goiter (3), colloid adenoma (5), and multinodular colloid goiter (1) showed definite regression of toxic symptoms after one or two weeks of administration of Lugol's solution. We did not give thiouracil to pregnant patients because undesirable side effects on mother and fetus have been reported in the literature.^{1, 9, 17}

Operation.—In the majority of cases (20) bilateral subtotal thyroidectomy was performed. In 6, lobectomy was done, and in one case arterial ligation only. Ten patients underwent thyroidectomy in the third month of pregnancy, 6 in the fourth month, 5 in the second month, and 3 in the first month. Only one patient was operated upon in the eighth month. The only death in our series was that of a 31-year-old patient with slight exophthalmos, a pulse rate of 196, and severe vomiting of pregnancy. She had lost 25 pounds during pregnancy. Lobectomy was performed in the third month of pregnancy for a colloid adenoma. The immediate postoperative course was uneventful in the hospital, and she was discharged markedly improved on the tenth day. She died of heart failure and respiratory infection two months later.

Follow-up.—Spontaneous abortion occurred in a 3 months' pregnancy, 9 days after thyroidectomy. One patient, after removal of a toxic diffuse colloid goiter, gave birth prematurely to a living child. In another premature delivery of a patient with nodular colloid goiter the baby lived only a short time. One patient with toxic colloid adenoma had a stillborn child following thyroidectomy. The only malformed infant, a Mongoloid child, was born to a 23-year-old patient with diffuse and adenomatous toxic colloid goiter. In 23 cases, pregnancy proceeded to term uneventfully.

Recurrences.—A 34-year-old patient, who had a toxic colloid nodular goiter removed, developed toxic symptoms, especially cardiac complaints, after two following pregnancies. A 28-year-old patient had a mildly toxic diffuse colloid goiter removed during the third month of pregnancy. She was well for $1\frac{1}{2}$ years, then lost 15 pounds, became nervous, and suffered from tachycardia. A 21-year-old patient had a bilateral thyroidectomy for exophthalmic goiter, and remained well for 6 years after operation when the neck began to enlarge again without causing toxic symptoms. The blood protein iodine at this time was 5 μ g and operation did not seem indicated. In 24 cases, no recurrence was noted.

Pathology.—The weight of the surgical specimens varied between 25 and 426 grams. The weight of the exophthalmic goiters was between 24 and 44

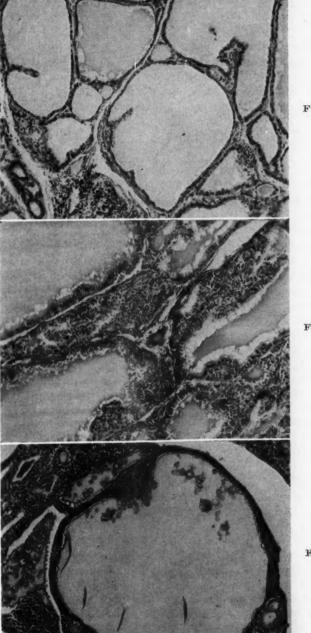


Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Diffuse colloid goiter, 42 grams, of a 31-year-old patient, four months' pregnant. Goiter had been noticed since the first month. No eye signs, nervousness, tremor, or rapid heart. The follicles were wide and contained thin colloid. The epithelium was cuboid.

Fig. 5.—Exophthalmic goiter, 44 grams, of 18-year-old primipara. Operation in second month of pregnancy. Patient had lost 10 to 12 pounds in spite of great appetite. The papillary epithelial proliferation is evident.

Fig. 6.—Colloid adenoma in right lobe of goiter of 38-year-old patient, four months' pregnant. Patient lost 40 pounds. Some epithelial proliferation and areas of thyroiditis are noticed.

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grams, of the diffuse colloid goiters between 35 and 42 grams. The multinodular colloid goiters had a weight of from 155 to 426 grams. The weight of the colloid adenomas varied between 35 and 174 grams.

In 6 instances the histologic diagnosis was exophthalmic goiter (Fig. 5); in 5, diffuse colloid goiter (Fig. 4); in 2, fetal (small follicular) adenoma. Foei of chronic thyroiditis were found in 11 of the 27 goiters, an incidence of 40.7 per cent. It occurred in 4 exophthalmic goiters, 4 diffuse colloid goiters, 2 colloid adenomas (Fig. 6) and 2 cases of nodular colloid hyperplasia. In comparison, in a series of 75 nonpregnant patients, 65 per cent of the surgical goiters showed areas of thyroiditis.

The Function of the Thyroid in Pregnancy

While it is well known that during pregnancy the thyroid gland often becomes enlarged, there is no agreement in regard to its functional significance. Seitz, of in 1913, saw evidence of increased thyroid activity in the high iodine content of the blood, in the elevated basal metabolism, and in the clinical experience that toxic goiter often becomes worse during pregnancy. The opposite view was held by Knaus. Increased storage of iodine-poor colloid in the thyroid during pregnancy, low urinary excretion of water and sodium chloride, nitrogen retention, and decreased resorptive capacity of subcutaneous tissue suggested to him a low thyroid function. Breitner of Austria and Küstner of Germany accepted this view.

Several investigators^{8, 11, 19} have found that the protein-bound iodine of serum rises sharply during pregnancy and returns to the normal range after delivery. Bokelmann and Scheringer³ were the first who determined the blood iodine level during pregnancy. In 43 pregnant women, in the second month of pregnancy, they found high values which steadily increased to the seventh month. Heinemann and co-workers¹¹ determined the serum precipitable iodine in 43 pregnant women. In normal pregnancy the serum iodine ranged from 6.2 μ g per cent to 11.2 μ g per cent as early as the third week. It remained high during the subsequent months and subsided only after delivery.

Russell¹⁹ studied the PBI in 60 pregnancy cases and found in normal pregnancy a PBI above 6.0 μ g per cent after the tenth week. The highest level in his series was 10.8 μ g per cent. Danowski and associates⁸ studied the level of PBI in normal pregnant women during the second and third trimesters. The average PBI value in pregnant women was higher than in nonpregnant women. The highest value found in normal pregnancy was 11.3 μ g per cent.

We determined the protein-bound iodine in 31 pregnant women; in 25 of these, thyroxin levels were also determined. Our method of determination of PBI was that of Barker; the serum thyroxin was determined by Danowski's method. The technique and results of these tests on more than 200 patients have been published previously. Thyroxin and PBI determinations in 79 adults without hyperthyroidism served as controls. In most instances the pregnancies were free from complications and terminated in the delivery of a living child at term. There were only 3 abortions and one delivery by cesarean section of a stillborn infant.

The average value of PBI in pregnancy proved to be higher than in non-pregnant individuals. In more than 400 controls, we found a normal range of from 3.2 to 6.2 μ g per cent. In 11 of our patients the values were above the upper limit of the normal. Our highest value observed was 11.2μ g per cent. The serum thyroxin during pregnancy ranged between 2.2μ g per cent and 5.7μ g per cent, averaging 4.0μ g, while the average was 3μ g in the controls. Our

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studies confirm the reports by Heinemann,¹¹ Russell,¹⁹ and Danowski,⁸ on the elevation of the PBI level during pregnancy. In accordance with Danowski's observations, this rise is associated with an increase in serum thyroxin.

Increased Demand for Thyroid Hormone During Pregnancy

Bodansky and Duff² studied the influence of pregnancy on the resistance to thyroxin and found that following daily administration of 1 mg. of thyroid extract, nonpregnant animals will lose weight rapidly and often die, while pregnant rats tolerate it easily. This suggests a greater need for thyroid hormone during pregnancy. These observations were confirmed by Danforth and Loumos⁷ in 1936. After giving 10 mg. thyroxin to pregnant white rats they did not observe any increase in oxygen consumption or loss of weight as in the control animals.

Mahaux¹⁸ stated that during pregnancy myxedematous patients require much more thyroid extract to maintain normal thyroid function than without pregnancy. He sometimes had to increase the daily dose up to 1 Gm. or more. We observed one case of pregnancy in myxedema which confirms Mahaux's observation.

Case Report.—Mrs. D. F., a 25-year-old white woman, complained on Nov. 14, 1934, of goiter for 1½ years, with choking sensation, nervousness, palpitation of the heart, and moderate edema of the face and ankles. The symptoms became worse during menstruation. The blood pressure was 136/74, the pulse rate 94. The thyroid was easily palpable. On May 29, 1935, she complained of sleepiness, shortness of breath, and feeling cold. The skin and hair were dry. Her weight increased to 172 pounds. The thyroid appeared to be nodular. She received 1 grain thyroid extract daily until February, 1936, at which time she weighed 186 pounds, was tired, sleepy, and short of breath. The menses were regular, lasted 2 to 3 days, and were scant. The basal metabolic rate was 15 below normal. She received anterior pituitary extract, 4 grains three times daily. The body seemed to swell a week before menses.

On April 7, 1936, a bilateral thyroidectomy was performed. The gland was enlarged, without nodes, the cut surface was grayish brown, the consistency was firm. Microscopic examination showed many lymph follicles with germinal centers. Most follicles were of medium size and contained well-stained colloid with few vacuoles. There were many follicles without colloid but containing groups of macrophages. Only occasionally oxyphilic cells were noticed in the follicle wall. The histologic diagnosis was lymphadenoid goiter.

After the operation the patient gained 10 pounds, the hands and ankles became swollen, she felt tired and sleepy much of the time. Her weight was 195 pounds, the pulse 70; she lost hair, the skin was dry. She received 2 grains of thyroid extract daily. Early in 1937 the patient became pregnant and her symptoms of myxedema became more pronounced. The thyroid medication had to be increased to 8 grains to keep her comfortable. The basal metabolic rate was 10 per cent below normal. The pregnancy was undisturbed and on Nov. 25, 1937, a normal female child was delivered.

This case, which required during pregnancy four times as much thyroid extract as before or after pregnancy, supports the view of Mahaux that during pregnancy the organism requires much more thyroid hormone than without pregnancy. The clinical as well as the experimental observations that in pregnancy high doses of thyroid extract are tolerated would explain the fact that thyrotoxic symptoms during normal pregnancy are lacking, in spite of a high basal metabolism and high protein-bound iodine level.

Conclusions

1. Anatomic study of 65 autopsy thyroids from pregnant women disclosed that the incidence of goiter is not greater during pregnancy than in the general population.

- 2. Actual measurement of the size of follicles and height of epithelium in these 65 glands and comparison with the measurements in 47 thyroids from nonpregnant individuals of the same age revealed that, as a rule, during pregnancy the thyroid has large follicles with abundant colloid and at the same time definite signs of cellular hypertrophy.
- 3. Determination of protein-bound iodine and thyroxin in the serum of pregnant women showed a trend toward high values, with PBI values reaching $11.2 \mu g$.
- 4. The lack of thyrotoxic symptoms in spite of a higher activity of the thyroid during pregnancy can be explained by a greater demand for, and greater toleration of, thyroid hormone, as demonstrated by a patient with postoperative myxedema who became pregnant.

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DYNAMICS OF THE AMNIOTIC FLUID AS MEASURED BY CHANGES IN PROTEIN PATTERNS

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s in Feb. ZOLTON T. WIRTSCHAFTER, M.D., AND DAVID W. WILLIAMS, M.D., PORTLAND, ORE.

(From the Research Laboratory, Veterans Administration Hospital, Portland, Oregon, and the University of Oregon Medical School)

AMNIOTIC fluid has been referred to as a "private aquarium" for embryos of air-living forms, in which recapitulation of the water existence of ancestral forms occurs. To this fluid has been attributed the protection of the embryo, not only against mechanical injury, but also from adhesions and consequent malformations. This concept of the sea-water bath, picturesque as it is, inadequately conveys the complex components of this amniotic fluid which is now found by means of electrophoretic studies to contain the protein building blocks of life. In view of this fact, and the further consideration that a review of the available literature does not contain a record of the weight changes of the amniotic fluid, fetus, and placenta, together with electrophoretic studies of the changing protein composition of rat amniotic fluid during each of the successive days of the gestation period, these data have been determined and recorded.

Methods

Environment.—The experimental animals were housed in an air-conditioned room in which the temperature was regulated at 73 to 75° F. and the relative humidity at 45 to 50 per cent.

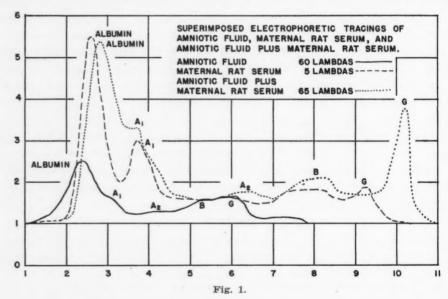
Diet.—The diet of the animals consisted of: whole wheat 67.5 per cent, casein 15.0, whole milk powder 10.0, iodized salt 0.75, calcium carbonate 1.5, and hydrogenated vegetable oil 5.25 per cent. A concentrate of fish oil in an amount to give 1.5 chick units of vitamin D and 10.5 U.S.P. units of vitamin A per gram was included in this diet.

Animals.—Thirty-three adult female rats of the Long-Evans strain were used in this experiment. The day of conception was determined by means of the vaginal smear technique and the time of parturition calculated from this initial finding. Vaginal smears were examined microscopically daily from the time of conception to the day of implantation. Invariably, in normal rats, the presence of red blood cells denoting implantation was observed on the twelfth or thirteenth day of gestation.

Autopsy.—All autopsy procedures were performed with rats under ether anesthesia, and a detailed inspection was made of all viscera. Particular attention was focused upon the uterus. To allow comparative quantitative evaluation of the gestation process, color photographs were made of the uterus, placentas, and embryos, following the removal of the normal embryos by cesarean section. The individual total weight of the embryo was first determined. This weight included the placenta, fetus, amniotic fluid, and the fetal

membranes. The amniotic fluid was then removed by a sterile syringe and needle, and the placenta and fetus were separated. After the excess moisture was blotted on a filter paper (fluid which could not be removed), the weight of the fetus and the weight of the placenta plus the fetal membranes were determined. The weight determinations were made on a Roller-Smith precision balance. However, the older fetuses were weighed on a tension balance.

Electrophoresis.—Paper electrophoresis was performed with a Spinco Model-R apparatus and the stained, dry strips were evaluated with the Spinco Analytrol recording scanner and integrator. Each run was for a period of 20 hours at room temperature (27° C.). Daily electrophoretic determinations were made of the amniotic fluid and maternal serum during the gestation period. For this purpose (1) 60 lambda of amniotic fluid, (2) 60 lambda of amniotic fluid with 5 lambda of maternal rat serum, and (3) 5 lambda of maternal rat serum were placed on Whatman No. 3 MM paper, with a sodium



diethylbarbiturate buffer of pH 8.6 and an ionic strength of 0.75. A current of 5 Ma, was employed throughout. It was necessary to utilize a 60 lambda sample because of the low protein concentration of amniotic fluid. To localize and to determine the various protein components of amniotic fluid, 5 lambda of maternal rat serum were added to 60 lambda amniotic fluid samples (Fig. 1). For determining the serum protein components, 5 lambda of maternal rat serum were utilized. In this manner, the total protein, albumin, and the globulin components of amniotic fluid could be determined for each day of gestation from the twelfth to the twenty-second day.

Results

Amniotic fluid is not available in sufficient amount for determination by electrophoresis until the twelfth day of gestation. The amount of amniotic fluid during the gestation period increases from the twelfth day to the eighteenth day. There is a decrease in the amount of amniotic fluid during the remaining 4 days of the gestation period. The weight of the placenta

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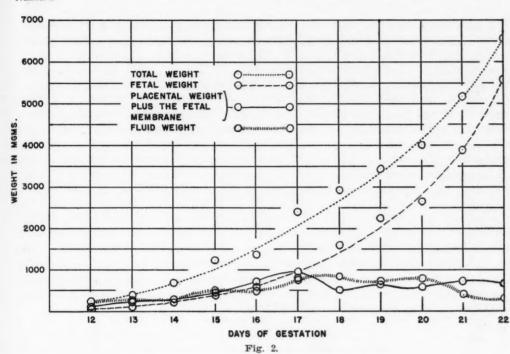
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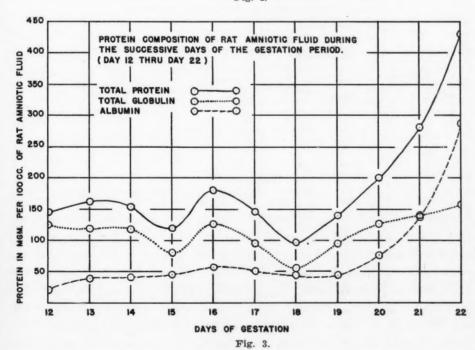
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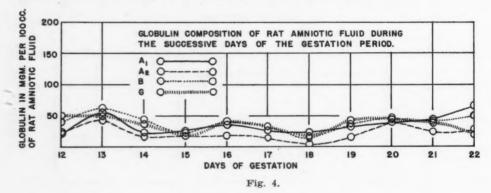




nearly equals that of the amniotic fluid, except at termination of the gestation period. There is a marked increase in the weight of the fetus on each successive day during the entire gestation period (Fig. 2).

The total protein of the amniotic fluid, which is composed of albumin and globulin fractions, fluctuates throughout the entire period of gestation. From

the eighteenth day through the twenty-second day of the gestation period, there is a marked increase in all protein components. Unlike serum protein levels, amniotic fluid contains a higher concentration of globulins than albumin until the twenty-first day of gestation (Fig. 3). The albumin concentration increases in greater proportion than the globulin from the nineteenth day on, so that the concentration of albumin exceeds that of the globulin at the end of the gestation period, i.e., the twenty-second day. On the twentyfirst day of the gestation period, the total protein of rat amniotic fluid is 280 mg. per 100 c.c., the albumin component is 140 mg. per 100 c.c., and the total globulin is 140 mg. per 100 c.c. of amniotic fluid. On the twenty-second day of the gestation period, however, the total protein of amniotic fluid is 430 mg. The albumin component is 270 mg. per 100 c.c. and the total globulins are now 160 mg. per 100 c.c. of amniotic fluid. The increase in total protein at the termination of gestation is due almost entirely to the albumin The albumin-globulin ratio at the termination of gestation is greater than the albumin-globulin ratio of the normal adult rat serum. The globulin distribution curve indicates a slight increase in the alpha₁ globulin component at the termination of the gestation period. Caution must be exercised in this interpretation, because the alpha, globulin migrates in proximity with the albumin component electrophoretically (Fig. 4).



Comment

For at least a hundred years, investigators have attempted, through physiologic and clinical experiments, to trace the spring and outlet of the amniotic fluid. Among the most definitive studies made have been those of Vosburgh and associates.¹ These present what appears to be important evidence that the water in the amniotic fluid is replaced from maternal plasma every 2.9 hours. It is assumed that an equal amount of water is transferred in the opposite direction, from amniotic fluid to mother, thus producing a continuous exchange of water between these two compartments. Rosa² stated that there is evidence of secretory potentialities in the amniotic epithelium, but so far there has not been demonstrated sufficient activity of this kind to account for the formation of large volumes of fluid. Other investigators have attributed this fluid in part to fetal micturition—many have referred to it in terms of "a transudate," and still others as a "dialysate." Hutchinson and his co-workers³ utilized transfer rates of sodium, potassium, and hydrogen isotope

tracers to find that the amniotic fluid is not a "transudate or dialysate of maternal plasma," but "that each element exchanges at its own rate and is in dynamic equilibrium with the maternal system."

The foregoing studies, which are of great interest and value in themselves, take no cognizance of the protein changes in the amniotic fluid during the course of gestation. To do so would be to note a higher concentration of globulins than albumin until the twenty-first day of gestation, and a dramatic reversal on the day prior to parturition. The increase in total protein at the termination of gestation is due almost entirely to an increase in the albumin components. The albumin-globulin ratio at the termination of gestation is greater than the albumin-globulin ratio of the normal adult rat serum. This cannot be attributed to a dialysate nor can it be derived from the maternal blood serum alone. The speculation, therefore, arises that the placenta, perhaps by some hormone mechanism, is involved in the elaboration and in the synthesis of this increment in the protein content of the amniotic fluid present at the end of the gestation period.

Summary

- 1. Rat amniotic fluid is more than a "sea-water milieu." It contains albumin and globulin protein fractions.
- 2. The albumin-globulin ratio of rat amniotic fluid at the termination of gestation is greater than the albumin-globulin ratio of maternal rat serum.
- 3. A higher concentration of the globulins than albumin is present in rat amniotic fluid until the twenty-first day of gestation. A dramatic reversal occurs on the day prior to parturition. Thus the total protein content of the fluid is greatly increased, and this increase is due almost entirely to the albumin fraction.
- 4. Amniotic fluid is not a transudate, is not a dialysate, and is not derived from maternal rat serum.
- 5. We suggest that the placenta, perhaps by some hormone mechanism, is involved in the elaboration and synthesis of the increased protein fraction.

We wish to thank Mr. Dean C. Altman, the head of the Photographic Department of this Hospital, for preparing the graphs, as well as Mr. Jimmy K. Tsujimura of our staff for his technical assistance.

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EVALUATION OF THE IODINE PREGNANCY TEST

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A SIMPLE, accurate chemical test for pregnancy would have obvious advantages over the usual biological methods with their limitations of animal supply, time involved, and relatively high cost. Many chemical tests have been devised and clinically evaluated, but as yet none of these is sufficiently accurate to be used with confidence as a diagnostic procedure, especially in the early stages of pregnancy. Recently considerable attention has been given to an iodine test as a simple and rapid procedure for detecting pregnancy.¹⁻⁵

Most investigators⁶ report that with known pregnancy urines not better than 80 per cent can be diagnosed correctly with this test, whereas the numbers of false positive reactions range from 19 to 44 per cent. While the results to date have been disappointing, certain features seemed worthy of investigation. The test requires only a few milliliters of urine and two minutes to complete. These properties, coupled with the fact that the nature of the substance in urine which reacts with iodine is still unknown, prompted us to a clinical and laboratory study of the method.

Materials and Methods

The urine specimens were submitted without history, by private physicians, to the Elizabeth Bio-Chemical Laboratory. The frog test, with the use of two frogs for each specimen, is routinely performed in this laboratory. Based on conclusive clinical verification of pregnancy, the frog test performed on 3,500 specimens during the past three years showed an over-all accuracy of 98 per cent.

The following procedure has been used generally by most clinical investigators: a tincture of iodine is added dropwise to 5 ml. of urine until an amber color is observed. The urine is then heated in a boiling water bath for at least one minute but no longer; the development of a pink to red color indicates a pregnancy or positive specimen. There is little color change in negative urine; in most samples the final color is light yellow.

The reagent is prepared by dissolving 2.0 Gm. of iodine and 2.0 Gm. of potassium iodide in 100 ml. of 50 per cent ethyl alcohol. The optimum amount of iodine is present when the starch-iodine test is positive, and when not more than 1 drop (0.05 ml.) of the reagent was used to achieve the change from a negative to a positive starch-iodine test. This is important since false negative results will occur when insufficient or excessive amounts of iodine are added to the urine.

The color complex given with iodine in pregnancy urine is sensitive to heat, and fades rapidly if heating is prolonged beyond the one minute specified. It is soluble and

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stable in amyl or butyl alcohol and, therefore, may be preserved by extraction with either of these alcohols within a few seconds after the reaction has been completed.

Results

During a period of three months, a total of 192 urine specimens were examined for pregnancy by the iodine test. The results of these tests were compared with routine frog tests performed on the same urines. The findings are summarized in Table I. Of the 110 urine specimens which gave a positive frog test, 18 per cent produced false negative tests by the iodine reaction. With the same method, 54 per cent of the 82 frog-negative urines gave false positive results. Many of the samples in the latter category gave a weakly positive reaction, but in a few urines a strongly positive test was obtained.

TABLE I. AGREEMENT BETWEEN THE IODINE TEST AND THE FROG TEST

	NUMBER OF TESTS	NUMBER OF IODINE TESTS AGREEING WITH FROG TESTS	% AGREEMENT
Positive frog tests	110	90	82
Negative frog tests	82	38	46

In view of the large number of urines which were diagnosed incorrectly by the iodine test, studies on the importance of pH and specific gravity in this reaction were undertaken. Table II indicates that with the exception of the pregnancy urines which were diagnosed as false negative by the iodine reaction, the average values for specific gravity and pH of urines in the other categories were nearly identical.

TABLE II. COMPARISON OF SPECIFIC GRAVITY AND pH OF URINES DIAGNOSED BY THE FROG AND IODINE TESTS

	NUMBER OF URINE SPECIMENS	SPECIFIC GRAVITY	pН
Frog positive	100	1.020 ± .007*	6.05 ± .51
Frog negative	82	$1.020 \pm .007$	$6.0 \pm .48$
Iodine positive	134	$1.020 \pm .006$	$6.1 \pm .54$
Iodine negative	58	$1.018 \pm .008$	$5.9 \pm .58$
False positive iodine	44	$1.020 \pm .006$	$6.0 \pm .42$
False negative iodine	20	$1.015 \pm .007$	$6.5 \pm .65$

*Standard deviation of the mean.

In the false positive iodine group, many samples of high specific gravity gave a negative chemical test following dilution with water to a final specific gravity of 1.010. Although in this category this procedure leads to a better correlation with the results in the frog test, it would fail in urines of high specific gravity with weakly positive reactions which agreed with the biological test. In addition, it could not be expected to change the results in urines of low specific gravity.

In the small number of specimens in the false negative iodine group, the average value for specific gravity was lower and for pH higher than for all other urines examined. The results of the iodine test, however, were not affected when these urines were adjusted to pH 6, or when their low specific gravity was compensated for by the use of larger volumes of urine and concentration in 1 ml. butanol of any pigment formed.

By addition of various substances to negative urine it was determined that chorionic gonadotrophin, progesterone, pregnandiol, or estrogens (estriol,

estradiol, estrone) individually do not yield a positive iodine test. This is in agreement with the findings of other investigators. Baume has found that 3,4-dihydroxyphenyl derivatives, such as norepinephrine, arterenol, isoproterenol hydrochloride, and epinephrine, under these conditions, do yield a positive test with iodine. On the basis of these findings and the fact that the 3,4-dihydroxyphenyliodine chromogens can be extracted into n-butanol, similarly to the color complex found in pregnancy urine, Baum has suggested that a catecholamine or its metabolic derivative is present in pregnancy urine and is responsible for the iodine reaction. In our tests epinephrine, norepinephrine, and dopa reacted with iodine as described above, but the chromogens formed by these substances differ in some respects from the colored-iodine complex which is developed in pregnancy urine. For example, unlike the chromogen in pregnancy urine, the product of epinephrine and iodine (1) retains its color stability for a period of 3 hours in urine and for as long as 24 hours in pure solution, (2) develops rapidly at 40° C. to yield maximum color within one minute, and (3) is not completely extracted into butanol or amyl alcohol. The reaction product of dopa and iodine is extremely labile to heat and cannot be extracted into butanol or amyl alcohol. The iodine product with norepinephrine is not completely extractable in butanol and is less sensi-

The effect of pH on the density and stability of the iodine complex formed in pregnancy urine was investigated. One milliliter samples of pregnancy urine, adjusted to pH 4 to 9 in gradations of 1 pH unit, were each treated with 0.25 ml. of iodine reagent (5 drops) and heated for one minute in boiling water. Within 30 seconds, the chromogen was extracted from the aqueous phase into 5 ml. of n-butanol, and quantitative readings made in the Beckman colorimeter at $524 \text{ m}\mu$. In all of the samples of pregnancy urine tested in this manner, the concentration of chromogen was greatest at pH 7.0. However, between pH 5.5 and 6.5 the differences in density were slight, and since the urine specimens which we analyzed fell within this pH range, no adjustments were made. It was noted in these studies that the slight excess of iodine generally required for this test is not necessary for a positive reaction in urines

tive to pH changes than the active material in pregnancy urine.

brought to pH 7.5 or higher.

Comment

Our primary interest in the iodine test was to determine whether it is sufficiently dependable to be the basis for a rapid, routine test for pregnancy. The results in our laboratory yielded an over-all accuracy of only 64 per cent; the average figure for five other clinical studies¹⁻⁵ was found to be 72 per cent, the values ranging from 62 to 81 per cent. While these results rule out the use of this test for the present, it should be emphasized that identification of the substance in urine responsible for the test may be followed by modifications in the technique which could increase its reliability. Moreover, the very simplicity of the test as it is now performed allows for many improvements to be made in an attempt to reduce the number of incorrect diagnoses.

In common with our experience with other chemical tests for pregnancy, many of the urine specimens in the present study did not give clear-cut positive or negative reactions. This difficulty in reading the end point constitutes a serious source of error.

The test urines cannot be considered to have been obtained under optimal conditions. Even though we are not as yet aware of those factors which are

responsible for the incorrect results, greater accuracy might be expected if care were taken to assure that (1) the specimen was collected early in the morning before breakfast or at a standard time in relation to food intake, and (2) the urine was adequately preserved or kept under refrigeration until the test was run.

The urine specimens submitted to the clinical laboratory for pregnancy diagnosis were obtained mainly from patients in either of two categories: (1) women of childbearing age who have reason to suspect pregnancy and may be in the first trimester, and (2) older subjects who are uncertain as to whether or not they are beginning the menopause. In the former group, for a limited number of subjects who submitted urine within 6 weeks following the last menstrual period, the iodine test gave few false negatives, but out of a total of 10 specimens from patients entering the menopause, whose urine specimens gave negative frog tests, only 5 were diagnosed correctly by the iodine test.

Summary

A rapid, simple, and inexpensive chemical test for pregnancy based on the color reaction of iodine with urine is described. The dependability of the method was ascertained by comparing the results on 192 urine specimens by the frog and iodine tests. Of 110 specimens which gave a positive frog test, 20 were diagnosed incorrectly by the iodine test. Only 38 of the 82 negative urines by the biological test were correctly analyzed by the iodine reaction. The errors could not be corrected by adjustments in pH or specific gravity. In its present state of development, the iodine test is not sufficiently reliable to justify its use for the diagnosis of pregnancy.

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ASTHMA IN PREGNANCY

A Report of Seven Cases

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In THE United States of America there are about three and a half million people suffering from asthma, an incidence of 2.6 per cent.¹ Very little importance has been given to the disease as a complication of pregnancy, however. Derbes and Sodeman² reckoned that 0.4 per cent of pregnant women might be expected to suffer from asthma, a point substantiated by the figures from the Kings County Hospital, Brooklyn, where there have been 104 cases of asthma complicating pregnancy, labor, and the early puerperium in 14,800 deliveries during the period 1953 to 1955, inclusive, an incidence of 0.7 per cent. The adrenal steroid hormones are secreted at higher levels during pregnancy and it has been suggested that this might give a certain immunity against allergic phenomena.

A generally accepted classification of asthma in pregnancy was proposed by Green,³ who divides the syndrome into three main types, namely, pollen, ovarian, and a third group possibly sensitive to some product of conception. The pollen type of asthma according to Williamson⁴ is genetically transmitted. If the mothers suffered from asthma 58 per cent of the children developed asthma before the age of 10, while if both parents were afflicted 72 per cent of the children were affected. Included in this type are those pollen-sensitive patients in whom the attacks occur before pregnancy and are unrelated to the sex cycle. In this type pregnancy seldom exerts any beneficial or deleterious effects on the attacks.

Patients with the second type, or "ovarian asthma," have attacks, usually beginning during puberty and tending to occur just prior to, or during, the menstrual period. Green³ stated that these attacks may cease during pregnancy or lactation and reappear with menstruation. It thus appears that there is some hormonal influence in asthma, a relationship further suggested by certain animal experiments. Schäffer⁶ maintained that increased estrogen content in the body tissue augments tendencies to anaphylaxis in guinea pigs. Pasztor⁷ developed this idea further and suggested the administration of progesterone to neutralize the effect of excessive estrogen. These basic animal investigations were followed by studies in humans,⁸ in which the effect of endocrine products on allergic phenomena was determined. Skin tests were

performed for reaction to various hormones and then desensitization was carried out with gradually increasing doses of the offending hormone. Alternatively, therapy could be directed toward the elimination of the allergy-causing hormone by specific interference with its production. He concluded that there is present in man an allergic sensitivity to endogenous secretory products of the endocrine glands.

The effect of asthma on the fetus in utero has not yet been fully established and certain generally accepted facts need further elaboration and study. Derbes and Sodeman² stated that the incidence of abortion and prematurity is no higher in asthmatic pregnant women than it is among normal pregnant women (8.3 per cent) but that the fetal mortality is higher even though pregnancy entails little risk for the mother. Mayer⁹ reported 2 cases of fetal death in utero during asthmatic attacks of the mother in the sixth and eighth months of gestation. These observers believe, that although the maternal and consequent fetal anoxia is important, the three phenomena of the mother's asphyxia, peripheral hypertension, and a "toxic factor" probably combine to kill the fetus during acute attacks of asthma.

Although termination of pregnancy usually improves bronchial asthma, therapeutic abortion is rarely indicated. There have been no deaths reported in the recent literature and those that occurred in the past were probably caused by therapy which is now out of date. For example, today morphine is hardly ever used because of its depressing effect on the respiratory system but Williamson⁴ reported 2 deaths subsequently shown to have been caused by morphine. Jensen⁵ believed, however, that therapeutic abortion is indicated if the asthmatic patient has consistently suffered from acute exacerbations in all her previous pregnancies.

CASE 1.—Mrs. A. A., an 18-year-old white woman, gravida i, para 0, was admitted with a history of severe headaches, dizziness, scotomas, and generalized edema of 3 days' duration and dyspnea with wheezing of 24 hours' duration. The patient did not receive prenatal care.

On admission the patient was semicomatose, markedly dyspneic and orthopneic, and showed evidence of peripheral cyanosis with 4 plus edema of the feet, hands, and face. The pulse was 92 and the blood pressure 220/110. Râles, ronchi, and marked expiratory wheezes were heard throughout both lung fields. The uterus was enlarged to 3 finger-breadths below the xiphoid process. Palpation revealed the presence of twins. The cervix was 75 per cent effaced and a finger tip dilated and the membranes were intact with the head 1 cm. above the ischial spines. On admission a catheterized urine analysis showed 4 plus albuminuria.

Previous history revealed bronchial asthma of 7 years' duration prior to admission, with intermittent acute episodes. The last acute attack occurred 18 months ago. Therapy in the hospital included morphine 0.015 Gm. intramuscularly (one dose), magnesium sulfate 10 Gm. in 50 per cent solution intramuscularly every 6 hours, 1,000 c.c. of 10 per cent glucose and distilled water intravenously, and aminophylline intravenously. Eighty hours later the condition was essentially the same except that the urine was grossly bloody. Epinephrine was given subcutaneously and repeated every 3 to 4 hours. Hydrocortisone was administered intravenously 16 hours after admission in an effort to relieve the asthma.

Despite all treatment, 36 hours after admission the patient appeared semicomatose, the urinary output was rapidly diminishing, and the hematuria was more pronounced. It was now decided to terminate the pregnancy.

The membranes were ruptured artificially and a slow intravenous Pitocin drip was given. The patient was digitalized prophylactically. Labor did not ensue so that 3½ hours after the unsuccessful attempt at induction a lower segment cesarean section was performed under local 1 per cent procaine anesthesia. Two living 4 pound, 9 ounce infants were delivered. During the procedure the blood pressure dropped to 60/0 and a slow Neo-Synephrine drip was required to maintain an adequate blood pressure.

The respiratory condition improved dramatically following the cesarean section and the urinary output, which had measured 200 c.c. in the 14 hours prior to the cesarean section, began to increase. The blood pressure rose again to 150/90 and was maintained without vasopressors. Forty-eight hours after delivery the patient was well on the road to recovery and left the hospital on the thirteenth postoperative day. She was finally discharged from the outpatient clinic 3 months after delivery, looking and feeling remarkably well.

Case 2.—C. D., a 16-year-old gravida i, para 0, was seen in the prenatal clinic with a history of asthma of 4 years' duration, frequently requiring epinephrine for relief of attacks. Pregnancy was uneventful until the twenty-first week of gestation when she had an acute exacerbation which was relieved by "oral medication" and intramuscular penicillin. The patient was then hospitalized in the thirty-sixth week of pregnancy for a particularly severe attack requiring intravenous aminophylline, penicillin, ephedrine, potassium iodide, and Doriden.* The patient then was delivered by elective midforceps in the thirty-ninth week of gestation under caudal analgesia after 6½ hours of labor. No respiratory difficulty was experienced intra partum or up to 6 weeks post partum.

CASE 3.—C. M., a 27-year-old white woman, gravida ii, para i, had her first episode of bronchial asthma in the third month of her first pregnancy at the age of 26. She then had intermittent acute episodes including an intrapartum exacerbation. Sensitivity tests and desensitization were to have been done post partum but the patient became pregnant within 3 months of delivery and was told that desensitization would not be carried out because of possible risk to her self and to the fetus. The patient was asymptomatic until the last 2 weeks of her pregnancy when wheezing and dyspnea occurred. She was delivered under saddle block anesthesia in the thirty-ninth week of gestation by low forceps after a 7 hour labor. Acute exacerbations which occurred 38 and 96 hours post partum responded well to aminophylline and ephedrine and the patient was discharged asymptomatic on the seventh postpartum day.

CASE 4.—C. P., a 33-year-old gravida iii, para i, had her first acute attack of bronchial asthma at the age of 20 requiring intramuscular epinephrine and oxygen for relief. During the first full-term pregnancy at the age of 28 she experienced frequent attacks of asthma. The present pregnancy was uneventful until the thirty-second week when, following an upper respiratory infection, she noticed the onset of expiratory wheezing which improved on Tedral.† She then remained asymptomatic and was delivered at term by low forceps under saddle block anesthesia after a 3 hour labor. There was no intrapartum respiratory difficulty and the patient was discharged well on the seventh postpartum day.

Case 5.—A. R., a 23-year-old gravida iii, para ii, enjoyed good health until the third trimester of her first pregnancy when she developed allergic rhinorrhea. She had her first attack of asthma during the seventh month of her second pregnancy. The patient was asymptomatic until the twenty-seventh week of the third gestation when she had an acute exacerbation of asthma which responded to medication. She had another acute attack in the thirty-seventh week which also responded well. The patient was then delivered in the forty-first week of pregnancy by low forceps under caudal analgesia after

^{*}Doriden, alpha-ethyl-alpha-phenyl-glutarimide, CIBA, Summit, N. J.

[†]Tedral, theophylline, 2 grains, ephedrine hydrochloride % grain, and phenobarbital ½ grain. Warner-Chilcott.

4½ hours of labor. There was mild wheezing intra partum but no severe respiratory difficulty. She was discharged asymptomatic on the seventh postpartum day and referred to the allergy clinic for sensitivity studies.

Case 6.—R. McK., a 28-year-old white woman, gravida vi, para v, gave a history of bronchial asthma of 9 years' duration frequently requiring intramuscular epinephrine or intravenous aminophylline. She stated that there was slight improvement in her asthmatic condition during the first 5 pregnancies. In the fourth week of the sixth gestation she required hospitalization for acute asthma which responded well to epinephrine, aminophylline, oxygen, antihistamines, and phenobarbital. Sensitivity tests followed by specific desensitization were then carried out in the second and third months of pregnancy. Despite this the patient had 5 further acute exacerbations during the pregnancy, responding well to epinephrine each time. The patient went into precipitate labor in the thirty-seventh week of gestation and was delivered spontaneously of a living infant without anesthesia. There was no respiratory difficulty intra partum. She was seen 8 weeks post partum and apart from occasional wheezing she was free from symptoms of asthma.

CASE 7.—S. A., a 25-year-old white woman, gravida i, para 0, gave a history of asthma for one year prior to the pregnancy. The initial attack was precipitated by an upper respiratory infection and was relieved by Tedral, "injections," and aminophylline suppositories. The present pregnancy was asymptomatic until the fifteenth week when the patient required hospitalization for an acute exacerbation which responded to ephedrine, aminophylline, ammonium chloride, and phenobarbital. She continued to have mild, intermittent acute episodes. She was delivered in the fortieth week of gestation by low forceps under saddle block anesthesia after 7 hours of labor. There was no intrapartum respiratory difficulty and the patient was discharged asymptomatic on the seventh postpartum day.

Effect of Pregnancy on Asthma

It is believed that pregnancy does not alter or affect asthma. Jensen⁵ found in a series of 72 cases that allergic diseases improved during pregnancy in 39 per cent, remained unchanged in 19 per cent, and were aggravated in 42 per cent. Aggravation of allergic conditions may take place at any time during pregnancy but there is a consistency of reaction to the disease during subsequent pregnancies in each individual. If the patient is asthmatic the frequency and magnitude of attacks are no greater after the onset of pregnancy.⁵ It also appears unusual for a first attack of asthma to occur during pregnancy. This, however, is contrary to our own experience where in 4 of the 7 cases here repor⁴ed (Cases 1, 2, 6, and 7) the patients were hospitalized during pregnancy, 2 cases (Nos. 3 and 5) occurred for the first time during pregnancy, and another patient (No. 1) was hospitalized for asthma complicating acute toxemia of pregnancy.

Desensitization of asthma and other allergic conditions is widely practiced. Derbes and Sodeman² favored specific desensitization during pregnancy as there is no evidence of any effect on the fetus in utero and the incidence of anaphylactic reaction does not appear to be any greater than in the nonpregnant woman. In one case (No. 6) desensitization was carried out in the first trimester. The patient stated that she felt better as a result despite the fact that she suffered 5 distinct asthmatic attacks during the last 2 trimesters and required epinephrine on at least one occasion. However, she was successfully delivered of a normal infant without any further complications. Mayer⁹ believed that desensitization should not be done during pregnancy. One patient (Case 3) was not given this therapy on the basis that there was risk to the patient and her unborn infant.

Sheldon¹⁰ also believed that desensitization should not be done during pregnancy on the ground that histamine produces contractions of the uterine muscle, and acute allergic episodes or constitutional reactions occurring from desensitization injections result in elevated blood histamine levels. Furthermore, tolerance to allergic extracts may diminish during pregnancy; thus there is a risk in giving a pregnant woman what is normally her maintenance dose. Kapeller-Adler¹¹ has noted that if pregnancy is complicated by toxemia there is a rise in histamine in the plasma proportionate to its severity. This is caused by a fall in the histaminase level during toxemia, whereas the normal pregnant woman showed a rise. It appears therefore that the evidence for and against desensitization during pregnancy is conflicting and further investigation should be carried out before any definite conclusion can be reached.

The treatment of asthma during pregnancy should be the same as that given to the nonpregnant woman with the possible exception of desensitization which has already been discussed. When asthma occurs during pregnancy the usual precautions should be taken against exposure to allergic reactions and respiratory infections. One should also bear in mind that the psychic aspects of asthma are likely to be enhanced by the emotional factors of pregnancy. In labor the cardiac and respiratory symptoms may be embarrassed by an asthmatic attack, especially in the later stages when the stresses are greatest. Opiates are frequently used for the relief of pain during the first and second stages of labor, but as already mentioned should not be used on patients suffering from asthma. Barbiturates are commonly given during labor and there is no contraindication to their administration in the early stages. Some asthmatic patients are made worse by barbiturates, however, and in such cases hypnotic drugs such as paraldehyde and chloral hydrate should be used. Epinephrine and ephedrine are often used for the relief of asthmatic attacks, but these should be given with caution during pregnancy and labor because of their vasopressor effects, particularly if there is any evidence of toxemia.

ACTH and cortisone are frequently used in acute asthma or status asthmaticus, usually when all other methods of treatment have failed. Pregnancy complicated by toxemia is a contraindication to their use because they may cause hypertension and fluid retention of a nonallergic origin and possible renal damage. All bleeding states such as antepartum hemorrhage preclude their use. In Case 1 the situation was desperate so that despite the toxemia these substances were given. This particular case is an excellent example of two serious complications of pregnancy, namely, toxemia and asthma, requiring the paradoxical use of drugs. Medications commonly used in the treatment of asthma such as aminophylline, antihistamines, antibiotics, atropine, oxygen, and Alevaire* can be used effectively without any fear of their effects on the mother or baby during pregnancy and labor. The second stage of labor should be made as easy as possible, just as in cases of cardiac or other respiratory complications, and should be terminated therefore as soon as possible. Inhalation anesthesia should be avoided, and spinal, caudal, or local anesthesia should be used instead. However, local anesthesia is preferable because of the absence of hypotensive effects. Caudal anesthesia appears to have certain advantages in that it can be given in the early stages of labor and relieves anxiety and pain without interfering with the respiratory capacity of the patient.

^{*}Alevaire, an aqueous solution of oxethylated tertrary actylphenol-formaldehyde polymer 0.125 per cent in combination with sodium bicarbonate 2 per cent and glycerin 5 per cent. Winthrop Laboratories.

The indications for vaginal or abdominal delivery must depend on the particular condition of each patient. Cesarean section is usually reserved for cases where there is an obstetrical indication. Most asthmatic patients can be delivered per vaginam since it is rare to have asthma of such severity as to necessitate immediate delivery. Occasionally cesarean section is indicated in order to relieve respiratory embarrassment, especially if vaginal delivery cannot be accomplished within a short time. For example, in Case 1 a cesarean section was performed in order to relieve respiratory embarrassment provoked by an acute asthmatic attack and complicated by severe toxemia. In this case there was also increased intra-abdominal pressure from the twin pregnancy and dramatic relief of the respiratory symptoms followed evacuation of the uterus.

Summary

- 1. Seven cases of asthma complicating pregnancy are described.
- 2. The prophylaxis and treatment of asthma complicating pregnancy are discussed.
- 3. Attention is drawn to certain problems of treatment when asthma is complicated by pre-eclamptic toxemia.

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ADDITIONAL VARIATIONS OF THE SACRAL CURVES

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COMPLETE evaluation of the pelvis is of the highest importance to the obstetrician in his efforts to maximize the chances for an easy and atraumatic delivery. And, in appraisal of the pelvis, the sacral curve is an important consideration.

Greenhill¹ regards the sacral curve as highly significant in both normal and pathological labor. He feels this curve is involved in the labor mechanism which influences fetal movement along the birth canal. Neither he nor others had much to say of a specific nature about the importance of the sacral curve, however, until Mayer and Morin² focused their attention upon the particular obstetric significance of the sacrum. More recently, Roth,³ in the course of a series of pelvic examinations, turned his attention to the sacrum and the part it plays in the mechanism of descent and the management of childbirth.

Evaluation of the Pelvis and Curvature of the Sacrum

Roth cited six basic types of pelvic sacral curve to designate the variations of the sacrum. The purpose of these designations is to present a picture and not an absolute anthropological definition. Hence, the terms used are arbitrary. In addition, there is overlapping in the actual classification of a series of pelves. The pelvic sacral curve is seen only in the lateral roentgenogram of the pelvis.

This investigator points out that, in assessing and describing a particular pelvis, both roentgenographic and clinical information is needed. Relative diameters and capacity at the inlet and midplane, and the nature of the curve of the sacrum are brought out by the former method; the latter shows the relationship of the pubic arch, is chial spines, sacrospinous ligaments, side walls, and the position of the sacral tip in the posterior segment of the midplane.

Every piece of information is important in the attempt to avoid unnecessary sections and vaginal deliveries that turn out to be traumatic to both mother and child. Total evaluation of the pelvis, comprised of roentgen and clinical determinations, frequently enables the obstetrician to predict the most likely mechanism of descent and, in addition, offers him an insight into problems of positional dystocia as they may come up.

Two New Variations of Sacral Curvature

The six basic types of pelvic sacral curves presented by Roth are the following: Sickle, J-shaped, Hockey stick, Average, Shallow, and Straight (Fig.

1). In our work in Bellevue Hospital's Abnormality Clinic, we have observed two additional ones which we have designated the Bow and Knobby variations. These are presented in Fig. 2.

Bowing of the sacrum was seen in 6 per cent of the 1,044 patients in our series, studied during the period from July 1, 1949, through June 30, 1953, while the knobby sacrum was observed in 19 per cent. Thus, these two new variations occurred in a ratio of about 1:3, with the latter predominating.

The curvature of the sacrum has considerable obstetric significance. For example, when a sacrum is of the J, H, Sh or St type, the curvature of the sacrum cuts down considerably the space available in the posterior segment. Under these conditions, the operator must become aware of the need of performing the delivery through the anterior segment.

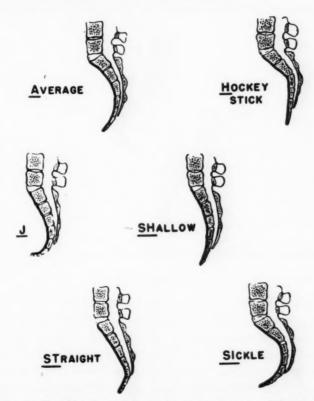


Fig. 1.—Classification of six basic sacral curves. (After Roth.3)

In our series, 17 of the patients, or 28 per cent whom we found to have sacral bowing, came to section, while 13 cases, or 21 per cent, were terminated by means of midforceps. Of the 198, or 19 per cent, with knobby sacrums, section was required in 37, or 19 per cent, and midforceps in 69 cases, or 35 per cent. In 2 of the 6 cases of failed forceps there was bowing of the sacrum. We wish to emphasize that these figures apply to the 1,044 cases studied in our Abnormality Clinic rather than to the entire series of 12,888 deliveries during that period.

Bowing of the sacrum, as shown in Fig. 2, presents a convexity in the middle of the sacral curve which per se is not the sole indication for operative

delivery. When this sacral variation occurs along with other architectural abnormalities of the pelvis in the same plane, however, it may very well be the factor contributing to dystocia.

The knobby sacrum may present false promontories in the lower third of the sacral curve. If the inclination of the sacrum is forward, the knobs may impede the descent and rotation of the vertex below the midplane. When the vertex becomes arrested in a transverse position, especially in a patient with a flat forepelvis, the operator may attempt application of the Barton forceps.

Although these forceps are ideal, the obstetrician may experience some difficulty in introducing the hinge blade because it sometimes is caught on a knob. Introduction of the blade can be made rather simple, however, by shifting it laterally to the sacral curve. In a local case which came to our attention, force was used to overcome the resistance of the knob and the blade fractured the posterior parietal plate of the fetal skull, resulting in stillbirth.

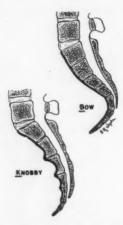


Fig. 2.—Two additional variations of the sacral curves described in the present article.

Comment

Labor in a questionable pelvis cannot be conducted solely on the basis of some method of measurement. Confronting the obstetrician are the problems of interpreting and evaluating pelvic capacity after the necessary measurements have been obtained, by any acceptable method. And these problems can be solved only by making use of the experience acquired over years of practice. It is of paramount importance that one become familiar with the forces of labor, its mechanism, and the conditions which may result in dystocia.

Summary

- 1. Two additional variations of the pelvic sacral curve have been presented. They are the bow and the knobby sacrum.
- 2. In a study involving 1,044 patients at Bellevue Hospital's Abnormality Clinic, bowing of the sacrum was observed in 6 per cent and the knobby sacrum in 19 per cent of the patients.
- 3. When bowing of the sacrum is present along with other structural abnormalities of the pelvis in the same plane, it may be the factor contributing to dystocia.

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4. If there is forward inclination in cases of knobby sacrum, the knobs may hinder descent and rotation of the vertex below the midplane.

5. Total evaluation of the pelvis profoundly influences the chances for easy and atraumatic delivery. Determination of the curvature of the sacrum is an important part of this evaluation.

6. The interpretation of the measurements of the pelvis and their application based on practical experience are essential in dealing with problems of dystocia.

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SEXUAL STERILIZATION

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A SURVEY of the pertinent literature on sexual sterilization for the past 25 years was undertaken with particular emphasis on the physical, psychiatric, and legal aspects. The three main types of sexual sterilization are as follows: (1) therapeutic, for medical indications; (2) voluntary, according to the patients' wishes; (3) statutory, as governed by certain states.

The aim of medical sterilization is to reduce maternal morbidity and mortality rates. Voluntary sterilization is to prevent pregnancy, usually for social and economic reasons. While it is an elective procedure, urgency may be a factor at times. Statutory sterilization is for the purpose of preventing procreation of individuals who suffer from mental disease, epilepsy, heredofamilial degenerative diseases, and criminal sexual psychopathy.

Sexual Sterilization in the Female

Here it should be noted that reports of the results of sterilization by x-ray or radium are not very numerous in the literature, hence they cannot be compared adequately with those of other methods.

Whitney¹ in 1929 reported on the castration of 11 females ranging in age from 13 to 39 years, with an average age of 23. The reasons were sexual perversion, obscene habits, boy craziness, excessive nervousness, and mental retrogression. Following the operation (salpingo-oophorectomy), Whitney wrote, "We had little or no trouble with our female patients after having established an artificial menopause."

Hackfield² in 1935 reported the effects of bilateral oophorectomy on 9 female habitual sex offenders in Switzerland. "The operation," he wrote, "was without effect upon either their psychic aberration or sexual disorder . . . sexual promiscuity and states of emotional excitement."

Watson⁴ in 1937 reported a study of sterilization in 172 females at the Sloane Hospital for Women over a 5 year period. Only one patient was deliberately sterilized as a procedure per se, in the absence of pregnancy or other gynecologic operations, and in

this case the x-ray method was used. The author made no mention of any postoperative consequence, except that 2 patients became pregnant following the supposed sterilization, which had been done in one case by resection of the cornu of the uterus and in the other by section of the middle third of the tube.

Popences in 1930 reported the following effect of salpingectomy in 105 female patients: an increase in sexual pleasure in some, no change in others, a decrease in sexual pleasure in several cases. He quoted an unpublished survey by Dickinson based on a large number of married women, excluding those who had never had sexual feelings, whose cases had been reported by 11 authors. The following postoperative consequences were observed: When both ovaries were removed surgically, sexual desire and response were lessened or extinguished. After a laparotomy for the removal of the uterus, tubes, or ovarian tumor, leaving one ovary, sexual desire was lessened or extinguished. Where menstruation was arrested by x-ray or radium, sexual desire was lessened or lost.

Woodside⁷ in 1949, in a study of sterilized married women of normal mentality living with their husbands, reported the following reasons for the operation, listed in order of frequency: anemia, weakness and exhaustion; multiparity; hemorrhages; miscarriages and ectopic pregnancies; cardiovascular conditions; various social reasons including those connected with the spouse; cesarean section; psychopathy, "nerves" and the like; varicosities, adhesions, uterine displacement, renal dysfunction; toxemia, hyperthyroidism, advanced age.

The effect on the menstrual function was as follows: menses unchanged in some cases, menses improved, menses worse, or disappearing, or lessened. Frequency of coitus was either unchanged, decreased, or increased. Frequency of orgasm was either unchanged, decreased, or more frequent. Three cases of frigidity following the operation are explained as being caused in one patient who was a Catholic by guilt feelings; the second patient was an unreliable informant, and the third, who was operated upon because of pelvic adhesions, had no pregnancies.

Vischi⁸ in 1951 reported that between June, 1940, and July, 1949, he electively performed 534 female sterilizations with no fatalities as a direct result. Spinal anesthesia caused the death of one patient before the incision, and another died of a heart attack 4 days postoperatively. In Vischi's opinion, sterilization does not promote promiscuity, which is an individual equation, but it does afford a sense of security by doing away with the dread of pregnancy.

Weinbaum¹⁰ in 1954, in a study of several hundred female sterilizations at the New York Hospital over a 20 year period, grouped the cases according to the various medical specialties. Two patients died after cesarean section done for heart disease, and a third after hysterectomy for purposes of therapeutic abortion.

The religious distribution in these cases was similar to that found by Fox¹¹ in 1940. Over half were Roman Catholics, about one-third Protestant, and about one-sixth Jewish.

Walker¹² in 1955 reported sterilization of women ranging in age from 17 to 47 years, over a 10 year period in a 200 bed general hospital in the Midwest. Thirty-three per cent were done at cesarean section and 56 per cent post partum. For some time, 4 living children had been considered by the hospital staff to constitute multiparity sufficient for sterilization. Now, however, 8 or more pregnancies are so regarded.

In comparison, one large general hospital¹³ in New York City has established the policy that there is multiparity sufficient for sterilization if the woman is 30 years of age and has 6 living children, or 35 years of age with 5 living children, or 40 years of age with 4 living children. Still another large general New York City hospital¹⁴ decides whether sterilization is indicated on the circumstances of the given individual, although factors of age and number of children are taken into consideration.

The Commissioners of the Joint Commission on Accreditation of Hospitals¹⁵ "feel that this is a question that can only be solved at the local level because of the feelings of the community; religion, physicians and the hospital itself all should be taken into

consideration. The ruling of the Joint Commission on these matters therefore is that they must always have consultation and the hospital allowing these procedures must have rules and regulations that will be followed by the medical staff."

Sexual Sterilization in the Male

Since sterilization of the male is an easier and much less hazardous operation than it is in the female, the question is often raised as to why devoted husbands do not submit to the procedure out of kindness to their wives. Watson⁴ stated that in his entire professional experience only one—a medical man—made this choice. In this connection, Tolen¹⁶ wrote that in 25 years of obstetrical practice he never had occasion to refer a husband to a urologist for vasectomy.

Steinach¹⁷ in 1927 credited his group in Vienna and Benjamin in New York with being the first to prove that high blood pressure decreases considerably after vasoligation, rising again only slightly after a few months, so that a relatively reduced blood pressure persists. "As a result of the dilation of the blood vessels, which is recognized by the reddening of the previously pale buccal mucosa (gums) and of the exposed parts of the skin (ears and membranes between the fingers), the sensation of coldness of the hands and feet disappears; the turgor improves; the general appearance becomes healthy."

Steinach further reported that he demonstrated histologically that vasoligation lavishly produces a cycle in growth of tissue of the male generative gland by causing the expansion of the interstitial tissue at the expense of the generative tissue within the entire gland. In the course of a few months, the generative tissue undergoes complete generation, so that the histological aspect of the vasoligated testicle about 6 months later corresponds to that of a normal one.

Popenoe¹⁸ reported the following results on 6,255 sterilized patients, male and female, of whom the insane were 3 times as numerous as the feeble-minded. In his opinion, none of the patients was fit to be a parent and his or her attempt to bring up children would be disastrous to the patient and even more so to the offspring.

Of the patients released from psychiatric hospitals, 6 out of every 7 were either indifferent to the operation or pleased that it had been done. One out of every 7 was dissatisfied, but gave no rational reason. No instance was found where a family had been broken up or there were any untoward results. On the contrary, Popenoe wrote, "In case after case the operation was the only thing that enabled a family to be kept together and the patient to remain in the community instead of returning to the state hospital."

Applebaum¹⁹ reported that, without knowledge of the law in New York State, he performed sterilization on 3 inmates at the Rochester State Hospital. In June, 1925, the legality of his operation was questioned, a negative decision was made by the attorney general, and Applebaum was forced to discontinue the operation.

The stories of the Kallikak and Juke families, as reported by Applebaum, are of unusual interest. Martin Kallikak, a young Revolutionary soldier of good family, mated illegitimately with a feeble-minded girl. The 480 descendants included 143 feeble-minded persons, 36 illegitimate, 35 sexually immoral, 8 keepers of brothels, and 83 babies born so feeble that they died in infancy. Later in life Kallikak married a young Quaker girl of good ancestry and they produced a line of 496 normal people.

Max Juke was a lazy, shiftless New England vagabond, born about the year 1729. Eventually he married and settled in New York State. His two sons married two sisters who were both mentally defective. About 1,220 descendants were reported up to 1915. Of these, 300 died in infancy, 310 were professional paupers, 440 were ruined by disease, 50 were prostitutes, 60 thieves, 7 murderers, and 53 criminals of various kinds.

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Whitney¹ made the observation that follows about 11 vasectomized and 9 castrated (orchidectomy) males, the youngest being 12 and the oldest 31 years of age. In comparison with females, the castrated males as a rule changed more rapidly. There were no observed serious effects on the health due to the sudden removal of the internal secretion of the testicle.

Peterson²⁰ in 1920 reported an experience similar to that of Applebaum,¹⁹ in which the governing body of the University of Michigan was asked to discipline him for sterilizing an imbecile girl with a contracted pelvis at the time of a cesarean section. Like Watson and Tolen, Peterson found only one male who requested vasectomy and "there was a question in his case whether he was quite right mentally." The author was opposed to what he called "lay propagandists" for sexual sterilization, believing it should apply to men as well as women.

Popenoe,²¹ in 1930, reviewing written case histories of a psychiatrist in private practice, observed that these patients "are found to marry as often as the rest of the population, though they cannot adjust as is shown by the excess of divorce over the average; the number of children is the same as in other groups of similar economic and social status; children born may be handicapped by defective heredity and even if normal these children, brought up by psychopathic parents, will have undesirable conditions of mental hygiene." Popenoe does not offer an explanation for his statement that "in all suicides, men usually outnumber women by the ratio of 3 or 4 to 1."

According to Thompson²² in 1935, the alarmist propaganda of those years that mental deficiency and disorders were greatly on the increase was false. He believed sterilization of known mental defectives would have but little effect in reducing mental deficiency because only 5 per cent of mental defectives have a mentally defective parent, and sexual sterilization could be used only as an adjunct to prevent the procreation of unstable stock.

Hackfield's² report on the female castrate has already been noted. In 25 nonpsychotic male sex offenders, bilateral orchidectomy was productive of an immediate and lasting cure in most of the cases, and a somewhat retarded cure in 3 instances, without any marked physical or mental sequelae. This was a spectacular result in view of the absence of positive therapeutic value in the female castrate (oophorectomy).

In 6 male psychotic patients, bilateral orchidectomy was without effect upon either the psychic aberration or the sexual disorder. Hackfield believed the therapeutic action was due to a reduction of somatic sexual tension by the removal of the sex glands. He made no attempt, however, to explain why the female castrates were not similarly improved, except to say that the libido has a psychic component and derives energy from other physiological sources, especially the adrenal glands.

Recommendations of Committee of American Neurological Association

In 1935 the report of the American Neurological Association Committee²³ for investigating sterilization was published. Each year prior to 1935 the Quarterly Cumulative Index Medicus had listed numerous and various types of articles on sterilization. Since 1935 the number of papers on the subject has been drastically reduced, except for studies dealing with the obstetrical aspects. Having examined the statistics that were made available to it, the committee concluded, "... the rate of commitment for feeblemindedness and mental disease, when corrected for age, is not increasing in most of the cultural countries of the world." The committee believed this observation was substantiated by the lower marriage and higher divorce and reproductive rates in the mentally diseased and feeble-minded, as compared with the total population, especially in cases which tend to be hereditary.

Further findings were as follows: The death rate in all forms of mental disease and feeble-mindedness is higher than that of the general population. The sterility rate is higher in the mentally diseased and feeble-minded than in the total population. Marriage is a selective barrier, acting eugenically in

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so far as mental disease and defect are concerned. A high commitment rate and consequently the high cost of maintaining the mentally sick are not necessarily an actual increase in the cost of caring for the mentally sick and defective, since there is a community cost independent of commitment, and the social order is enhanced when insane and feeble-minded are institutionalized.

Regarding the genetic aspects, the committee believed that without the appropriate environment no genetic quality can express itself; that until and unless heredity can be shown to have an overwhelming importance in the causation of antisocial behavior, sterilization merely on the basis of conduct must be regarded as a "cruel and unusual punishment"; that the world would be poorer in persons of genius if certain of their psychopathic ancestors had been sterilized; that clinical experience and statistics indicated, at least in the case of manic-depressive psychosis, a certain hypomania often associated with great success and a warmth of character definitely valuable to society.

Further, the committee found that even among the feeble-minded there were individuals who were docile and industrious, and therefore invaluable as servants of society; that most of the legislation which had been enacted was based more upon a desire to elevate the human race than upon proved facts; that in the case of normal parents of one or more children suffering from certain familial diseases, such as Tay-Sachs amaurotic idiocy, sterilization may be considered; that the function of psychiatry was to discover pathology, pathogenesis, and therapeutics.

The committee recommended that sterilization be voluntary rather than compulsory; that the law apply not only to patients in state institutions but also to those in private institutions, as well as to those at large in the community, to avoid group or class discrimination; that adequate machinery for administering the law be set up; and that adequate legal protection for the members be secured by statute.

Sectional Reports

Lam²⁴ in 1936 reported on 300 cases of vasectomy performed from 1930 to 1936 in the outpatient clinic of Palama Settlement, Honolulu, Hawaii, as part of a birth control program. All the patients were on relief, but were supposedly normal individuals and active in community life. The operation was voluntary and the racial, religious, and age factors did not appear to interfere.

Postoperative complications were infection, hydrocele, and hematoma. One year after the operation and again four years after that, 85 per cent of the patients were examined. Two patients felt their sexual potency had been impaired, but in no case was there evidence of atrophy of the testes.

Craft²⁵ in South Dakota presented a follow-up study of 94 vasectomized defective individuals with a mean I.Q. of 58. His data conflict with those presented by the Committee of the Neurological Association. The percentage of mentally defective relatives of the patients was high enough to indicate a tendency toward a pronounced morbid heredity. The parents of the patients had an average of 6.2 offspring. The married patients had an average of 5.5 children per patient before sterilization, and since they were in their early thirties, it was believed they would have produced larger families. No sexual changes occurred as a result of the operation, and the ratio of sex offenses before and after sterilization was 7 to 1. This was attributed to better supervision following the operation.

De Vilbiss²⁶ in 1937 in Miami, Florida, reported 91 vasectomies during a period of several years on patients with low average intelligence, occasionally psychopathic, and frequently syphilitic. Like Steinach, she described marked blood pressure changes following vasectomy. When the patient's blood pressure is within normal limits, it may show a slight change either way. When low, it may show an increase. When high, it

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may show a steep to moderate reduction which is not permanent, but the subsequent increase does not reach the high reading before the operation. The author stated no explanation had been found to account for the blood pressure changes.

Lastrucci and La Piere⁵² in 1938, attempting to evaluate the subjective aftereffects of vasectomy on 52 San Quentin prisoners, concluded they could not be definitely determined. If the reported increase in libido after vasectomy could not be attributed to physiological changes, there was no justification for assuming the absence of adverse effects on the basis of the fact that only a relatively few of the patients reported a decrease in libido. The authors further stated that, aside from examination of the testes for atrophy, little objective research had been reported.

Butler²⁷ in 1945 related his experience in California from 1919 to 1943, during which time 4,310 male and female mentally defective patients were sterilized, with the indications regulated by compulsory statute. Seven deaths occurred but none could be traced directly to the operation. Of a total of 171 male epileptics sterilized, 140 had an LQ. below 90. The reason given for sterilizing the intellectually normal epileptic was the hereditary factors involved, and the frequent inability of those with epilepsy to care for their offspring. Three Mongolian idiots were sterilized only on the insistence of their parents.

The reasons given for sterilizing a large number of the patients who remained in the hospital were the occasional release for home visits, as well as the freedom allowed them within the institution. On the question of promiscuity, 9 out of 12 patients had been delinquent prior to commitment. After sterilization and return to the community on parole, only 1 out of every 12 was a sex delinquent.

Garrison²⁸ in 1950 reported vasectomies on 50 unselected mentally normal males in the State of North Carolina. Five patients were Negro, 45 white, ranging in age from 21 to 50 years. There were 19 patients with less than a high school education, 13 had been graduated from high school, 8 from college, and 10 from medical school. Forty-eight of the patients had at least one child, the average number of children being 3. A patient who had no children said his wife's "female trouble" kept them from attempting parenthood. The wife of the other childless person had 2 children, almost grown, by a former marriage and wanted no more. One man's wife bore him 14 children before he was operated upon.

As to the motives for vesectomy, 23 patients had as many children as they desired and could care for adequately; 19 had wives with physical disabilities, including kidney disease, diabetes, difficult labor, asthma, hydronephrosis, and eclampsia; in 8 cases the primary cause was a physical handicap in the husband—neurosyphilis, diabetes, rheumatism, multiple sclerosis, asthma, blindness, and deafness.

Three patients who were physicians reported discomfort in the early postoperative period. The other patients said there had been almost no pain immediately after the operation. A few noted mild discomfort some time later, tenderness in the testicles, dull aching with radiation from above the pubis into the scrotum after lifting heavy objects.

Regarding postorgasmal symptoms, one patient noted a feeling of fullness in the scrotum after orgasm during the first postoperative month, but not later. Another told of an occasional postorgasmal urge to void and slight urethral burning. The rest had no symptoms and experienced complete relief from sexual tension.

As to frequency of intercourse, 4 patients reported a decrease of sexual intercourse; one, a physician, ascribed this to "psychologic causes"; 8 patients had an increase in frequency, one patient explained this as being due to the newly found freedom from needing to use a condom, with the wife no longer fearing pregnancy; and the remaining patients reported no change. There were no changes in either external appearance or in sexual traits, such as pitch of voice or distribution of fat and hair. Three patients reported they regretted having had the operation and would undo it if they could.

Kallmann²⁹ believed "there is a tendency to stigmatize human genetics by identifying it with fatal trends or purposes. . . . One can strive for scientific dispassion toward

the moral, religious, or eugenic questions of psychiatry without rejecting them categorically merely because they are intangibles and do not lend themselves to exact measurement. . . .

"Eugenic methods of preventing conception are less objectionable than continence, rhythm, and non-completion of the sexual act... Surgical sterilization is unlikely to be demanded because contraceptive devices seem to gain steadily in popularity.... This trend will soon be intensified by the recently reported development of a safe antifertility drug called phosphorylated hesperidin."

Sieve³⁰ in 1952 reported the effectiveness of an antifertility factor in 300 fertile mentally normal married couples. A dose of 5 mg. of phosphorylated hesperidin for each kilogram of body weight plus an added amount to protect against possible loss from faulty absorption or excessive elimination, taken by both the male and female for 10 consecutive days, was necessary in order to achieve adequate blood level concentration. Omission by either partner for 48 hours necessitates another consecutive 10 day dosage. The drug is described as being without toxic or allergic reactions of any kind, even in high dosage.

Nelson³¹ in 1952 described his study of 21 males who had bilateral occlusion either from vasectomy, absent vas deferens, absent vas deferens and epididymis, or gonorrhea. He described the associated degree of peritubular fibrosis and spermatogenesis in each case, but it is not possible to assess his findings adequately from the information we now posess. He repudiated the validity of Steinach's observations by quoting the works of Schmidt,³² Moore,³³ Michelson,³⁴ Hotchkiss,³⁵ and Simmons.³⁶ Nelson concluded by stating that all 21 cases showed entirely normal secondary characters and there was no reason to believe their reproductive deficiency involved the endocrine component of the testicle.

A study by John³⁷ in Germany in 1938, however, presented an equal array of references and data on animal experiments showing microscopically visible changes in gonadal tissue following ligation of the deferent ducts. He believed the time span of other investigations was much too short, that the final results in animals (rabbits, guinea pigs, and rats) could not become available in less than twelve months.

Hammer,³⁸ in 1953, in a research project in the State of Virginia, applied sexual symbolism in a study of eugenically sterilized males. The result was that significant statistical differences of genital symbolization and castration feelings were found between the vasectomized patients and the controls (males operated upon for reasons other than sterilization, such as tonsillectomy and appendectomy). He suggested the need for investigation of a larger number of suitable cases before definite conclusions can be drawn.

George³⁹ in 1954 stated that one in every 165 liveborn babies in the general population has a major external malformation caused by defects in the germ plasm rather than by intrauterine factors, vitamin deficiencies, or toxins. Some disorders, he believed, are inherited from the parents; others are not inherited but are mutations, transmissible to the offspring. Some transmissible characters are known to be somatic dominants, others somatic recessives. Some are sex-linked dominants, others sex-linked recessives.

George presented the case history of a 27-year-old woman, highly neurotic, whose first child is an almost blind albino (hereditary and transmitted through recessive genes). A second child was stillborn with erythroblastosis fetalis. The woman is Rh negative, while her husband is Rh positive. According to Mendelian law, the chances are 25 per cent that any other child they might have would be an albino.

The author presented the following 4 possibilities in this case: (1) If nature is left to take its course, any pregnancy could result in albinos, stillbirth, early postnatal death, or feeble-minded offspring. (2) Sterilization could be done, ending reproduction for either or both partners. (3) If emotional attachment between the couple is not too strong, divorce and remarriage with another mate would produce normal children. (4) Artificial insemination could be performed with sperm from someone other than the husband. George believed the advising physician is on the horns of an ethical dilemma. Whichever course he prescribes, large groups of people are bound to consider it sinful.

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The Rise in Mental Disease

Malzberg⁴⁰ in 1955 quoted the most recent report issued by the National Institute of Mental Health for the United States, showing the increase in the number of patients under treatment in hospitals for mental disease from 150,151 in 1903 to 584,455 in 1951. Corresponding rates per 100,000 population were 186.2 and 386.8, respectively. Statistics for New York State show a rise from 15,473 in 1889 to 102,379 in 1952, with corresponding rates of 260.4 and 672.2 per 100,000 population.

In Malzberg's opinion, these data do not measure the rate of mental disease, but rather reflect an accumulation of mental patients in the hospitals from year to year due to the long average duration of hospitalization. To determine what trends may exist, it is necessary to ascertain the number of new cases. This means enumerating the number of new cases per unit of time in a unit of population. The only data available are the annual rates of first admissions to hospitals for mental disease, which definitely indicate a rise over long periods of time.

The trend is as follows in various diagnostic categories:

General Paresis.—The rate per 100,000 population decreased from 12.7 in 1920 to 3.0 in 1950, a reduction of 77 per cent. This decrease is due to more effective treatment of syphilis in the early stages, and reduction thereby of subsequent infections of the central nervous system.

Alcoholic Psychosis.—During the years of World War II, the number of first admissions and their corresponding rates dropped significantly, the rate in 1944 being the lowest in 20 years. Immediately after the war, however, the rate began to climb. It seems that psychological influences at work during wartime affect social behavior in such a way that the amount of general drinking is reduced, temporarily at least.

Psychoses With Cerebral Arteriosclerosis.—The increased incidence is accounted for by Malzberg on the hypothesis that those who survived to middle age a generation ago probably constituted a better selection than those who reach the same age periods today. Consequently, in corresponding age groups there is greater morbidity and mortality from degenerative diseases. Today, people in advanced age groups have a greater chance of developing a psychosis with arteriosclerosis. The chance of improvement leading to discharge from the hospital is less, and the chance of death greater.

Involutional Psychoses.—There is an increase from 7.4 in 1920 to 15.8 in 1930 to 22.2 in 1950—this, despite the fact that involutional depressions are being treated in large though undetermined numbers by shock therapy in the offices of private psychiatrists.

Manic-Depressive Psychoses.—There is a declining trend from 13.0 in 1929 to 5.5 in 1949. Since this began before the introduction of shock therapy, it appears probable that it is not a mere artifact.

Dementia Praecox.—There is an increase from 31.7 in 1920 to 37.6 in 1940, to 54.6 in 1950, a trend not due to the increase in the proportion of the general population who are of susceptible age.

The American Psychiatric Association Newsletter of December, 1955,⁴¹ reported the results of a survey made by a Canadian life insurance company on persons accepted for ordinary insurance after recovering from mental disorders. Applicants with a history of mild psychoneurosis had a survivorship rate of 99.1 per cent after they were insured 5 years, and 97.3 per cent after 10 years. These figures are only slightly lower than those of standard risks. After 15 years, among those with a history of severe psychoneurosis or psychosis, the survivorship rate was 88.8 per cent, with 93.1 per cent for standard risks as a whole. Suicide apparently accounted for the excessive mortality among former mental patients. For most other causes of death there was no significant difference.

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Legal Aspects

The first eugenic statute in the United States was passed by the Indiana legislature in 1907. Since then, 27 additional states have adopted various types of sterilization. Butler⁴² in 1951 reported that, of the 20 states which had no sterilization laws, 6 appeared not ready to accept such a program at that time. The other 14 states, mostly in the southern part of the country, were interested in a sterilization program and the enactment of an appropriate law.

As of January, 1955, a total of 57,218 official eugenic sterilizations were performed in the 28 states—34,282 on women and 22,936 on men. The grounds were mental illness in 44 per cent, mental deficiency in 51 per cent, and habitual criminality, epilepsy, moral degeneracy, and sexual perversions in 5 per cent.

During the past decade, the annual number of eugenic sterilizations has been decreasing from a yearly average of 3,000 in the thirties to 1,100 in recent years. This is partly due to a growing uncertainty as to the respective influence of heredity and environment in the genesis of certain types of mental disorder.

Stone⁴³ and Holman⁴⁴ reported an interesting opinion expressed by the Office of the Attorney General of Wisconsin in 1932 with respect to the legality of sterilization: "Even if we assume that the scientific and sociological should prevail, nevertheless, the law follows science in some fields by perhaps a generation, for the law can reflect the advances of science only when they have been accepted by the people generally.... The consequences to a physician from the performance of an operation of this kind, should the courts hold it illegal, could be serious ... until the law is settled, it is not prudent for a physician to perform a sterilization operation, except within the ancient field of surgery, viz., when it is a therapeutic measure."

In New York, one appellate court has stated an opinion⁴⁵ upholding a ban on the showing of a film on sterilization because "the content of the picture is devoted to an illegal procedure."

In 1912, in the State of New York, Dr. R. Bush introduced a sterilization statute, Chapter 545 of the Laws of 1912, which added Section 350 to the former Public Health Law. However, when the Public Health Law was recodified, this section was omitted. Meanwhile, the previous statute was declared unconstitutional 46 in 1918.

An unofficial and informal letter written by the Attorney General of the State of New York⁴⁷ in 1935 expressed the following view: "Due to the complications which may arise, the operation, if performed at all, must be undertaken only upon the strongest advice as to the necessity therefore from the attending physician and with the closest adherence to the legal procedure prescribed by your own attorney.

"At any rate, this is a perilous situation; because of the youth of the patient and the fact that the neurological clinic has found her to be definitely mentally deficient, even if the operation is performed only after all the proper consents are secured, the patient may, at some future date, become thoroughly dissatisfied that the operation was performed and may create a very complicated legal dispute."

An interesting case⁴⁸ is described in Minnesota where the surgeon performed a vasectomy on a patient whose wife, it appeared, could not survive another pregnancy. Thereafter, the patient resumed sexual relations with his wife and, in spite of the operation, she became pregnant. Though she survived the pregnancy, the husband was not satisfied, claiming the surgeon had guaranteed sterility, The pregnancy, he asserted, caused him great anxiety over his wife's health, and had put him to considerable expense. His suit for \$5,000 was based on the failure of the operation to achieve the promised results.

The court's opinion was as follows: "It is a matter of common knowledge that such an operation properly done in due course effects sterilization. Any competent physician or surgeon would have given advice to that effect. . . . The purpose of the operation was to save the wife from hazards to her life which were incident to childbirth. It was not the alleged purpose to save the expense incident to the pregnancy and delivery. The wife has survived. Instead of losing his wife, the husband has been blessed with the fatherhood."

The opinion⁴⁹ of the United States Supreme Court delivered in 1927 by Justice Oliver Wendell Holmes upholding sterilization served as a basis for formulation of statutes by several states.

"Eugenics" as a term was first used by Sir Francis Galton in 1883 to designate the reform movement introduced by him for improving the human race by scientific breeding. Yet the British still do not legally recognize eugenic sterilization today. In 1954, however, a wife appealed dismissal of her petition for divorce on grounds of cruelty—the cruelty being that her husband had had himself sterilized against her wishes. While the appeal was denied, the opinion was expressed that if the case had been tried in the court concerned with the administration of criminal law, without good medical reasons it "would be held to be a criminal offense, consent or no consent." Such a case, however, has yet to come before the British courts.⁵⁰

In 1934 Nissen⁵¹ presented his argument against including myotonia congenita among the diseases for which sterilization should be performed according to German law. He based his views on the belief that the disease is not a degenerative one, and is transmitted in a straight, dominant line. By implication, however, Nissen would make subject to the law the dominant homozygotic diseased members, from the hereditary but not degenerative aspects.

Comment

Official and recorded medical opinions regarding indications for strictly medical sterilization are fairly uniform, except for multiparity. As a result, in recent years there have been almost as many sterilizations for multiparity as for all other medical indications combined. If multiparity is placed in the category of voluntary sterilization, and there is considerable evidence to indicate that it belongs there, psychiatric and legal complications may occur much more frequently.

When the indication is a strictly medical one, religion is definitely not an obstacle. Psychiatric complications occur most frequently in emotionally unstable patients.

The indications for therapeutic sterilization in the female are fairly well established. The widest disagreement occurs in multiparity, in the number of cesarean sections sufficient for sterilization, and the degree of malignancy of neuropsychiatric diseases.

The indication for voluntary sterilization in the United States is chiefly an economic one. Limited income precludes proper rearing of additional children in families that are already large. Males are more apt to undergo voluntary rather than therapeutic sterilization. Statutory sterilization is usually referred to as eugenic sterilization.

In the female, postoperative physical complications range from benign to severe infections, thrombosis, pulmonary infarcts, pneumonia, atelectasis, and, occasionally, death. In the male, infections, abscess formation, and hydrocele are infrequent complications.

Psychiatric complications of therapeutic sterilization for strictly medical reasons, which rarely occur in a nonneurotic person, are sometimes due to the individual's emotional instability or orthodox religious affiliation. In general, however, religion is no deterrent to this type of sterilization.

Where sterilization is performed for socioeconomic reasons, particularly in the emotionally unstable individual, psychiatric complications occur more often. In the female, the menses become altered and may disappear, coitus may increase or decrease in frequency, orgasm frequency may decrease to frigidity, or there may be severe hypochondriasis. In the nonneurotic male patient, frequency of coitus, quality, and frequency of orgasm may be increased, unchanged, or decreased. Anxiety about castration occurs much more often in the male.

In statutory sterilization the psychiatric consequences vary, depending on the diagnostic category, sex, age, and the type of operation performed. In adult female sex offenders, bilateral oophorectomy was found to have no effect on their sexual disorder, sexual promiscuity, and state of emotional excitement. However, in preadolescent female sex offenders, bilateral oophorectomy brought about a reduction in sexual excitement and a diminution in perverse sexual behavior. In the adult neurotic female, morphine addiction occurs frequently following a castrating operation.

Nonpsychotic adult made sex offenders respond to bilateral orchidectomy much more favorably and without marked physical or mental sequelae. Bilateral orchidectomy in the adult psychotic male is generally without effect.

Legal complications of therapeutic sterilization for strictly medical reasons are rare. When they do occur, it is usually because of an unwanted pregnancy after the husband had been sterilized for a medical indication in the wife. In voluntary sterilization, however, legal complications arise more often out of the following circumstances: the physician was not protected by statute, the written consent of both husband and wife was not obtained, the children died as the result of a catastrophe, the operation caused a loss of sexual potency, or a surviving sterilized mate remarried and wanted more children. An outstanding legal complication in statutory sterilization led to the decision of the United States Supreme Court to uphold the legality of sexual sterilization.

From a strictly medical point of view, there are important advantages in sterilizing the male for an indication in the female. If selectively followed, there would be a further decrease in the maternal morbidity and mortality rates. Obstacles to this solution are the possibility of legal complications, plus the general reluctance of physicians to discuss this procedure with patients and their husbands.

The physical consequences of vasectomy have been declared practically nonexistent by most investigators. Following ligation of the different ducts in experimental animals, however, the observation of postoperative blood pressure changes, and the microscopically visible decomposition of testicular substance suggest a need for further investigation before vasectomy can be

safely recommended. The likelihood that phosphorylated hesperidin will further decrease the need for sexual sterilization is very doubtful in view of the requirement that frequent and prolonged dosage be strictly adhered to by both the male and female.

Evidence has steadily accumulated to show that intrauterine stress is more responsible for inborn anomalies than faulty heredity. It is believed that the incidence of inborn anomalies will be reduced when mothers are healthier during gestation. Nevertheless, the exact enzymatic nature of gene structure, how it is changed, and how the pathological changes may be corrected are critical and fundamental factors.

Until further light is shed on these matters, one viewpoint is that protection by sterilization and rehabilitation should be mandatory. Another opinion is that until the corrective measures have been determined, sterilization should be done only on a voluntary basis.

Summary

A survey of the pertinent literature on sexual sterilization for the past 25 years has been presented. Emphasis has been placed on the physical, psychiatric, and legal consequences in each of the 3 main types of indications for sterilization in the female and the male. The lack of uniformity of opinion indicates a definite need for more precise scientific information. The problem centers on the determination of how pathological mutant genes occur, and the exact chemical corrective measures.

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TRANSUTERINE TUBAL CAUTERY FOR STERILIZATION*

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S TERILIZATION of the human female remains a troublesome technical procedure requiring hospitalization, a general anesthetic, operating room facilities, and a convalescence of a week or more.

To obviate these problems, several attempts have been made to develop simpler techniques which would be effective. This report deals with our experience with modification of the Hyams technique, a transuterine tubal coagulation.

From the early attempts at tubal ligation by Blundell in 1819, through the era of intrauterine caustics, cautery, radiation, etc., and including the more recent biological attempts, no satisfactory method of sterilization has been found which is both reliable and without operative hazard. Direct surgical attack upon the tube has become the method of choice, but the variation of techniques from simple crushing to resection or total excision points out that no method is perfect in results.

Procedure

The present experimental procedure employed modification of the Hyams¹ technique—a method of performing transuterine sterilization with an instrument which he developed. As used by him this is an office procedure for the coagulation of the cornua by means of a high frequency current under direct vision with the fluoroscope.

The Hyams procedure was simplified to make it less complicated, less time consuming, and less expensive to the patient. The technical features, complications, and effectiveness of this technique have been evaluated.

First, the equipment was standardized so that a reproducible coagulation effect could be delivered under all circumstances. Following this, transuterine cornual coagulation was done on uteri removed at operation, not only to develop our sense of touch but to determine the desirable strength and character of the current necessary to accomplish coagulation.

The 45 patients selected for this study were grand multiparas who requested sterilization for social-economic reasons. As controls, 4 patients who were to have hysterectomy for other indications were subjected to this technique and the uteri removed at intervals of three, seven, and thirty days post coagulation. The uterine cornua were studied grossly and microscopically.

^{*}This study was made possible by a grant from the Human Betterment Foundation and through the cooperation of Dr. Clarence J. Gamble, Milton, Mass.

From these studies, it was apparent that in these selected cases the opening of the tube could be accurately located and destroyed by electrocoagulation

Following standardization of techniques and equipment 45 transuterine cauterizations were performed with the use of the modified Hyams^{1, 3} technique. A preliminary Rubin test was done. Morphine was employed as sedation in the first 7 cases, but this was found to be unnecessary, the patient experiencing no more discomfort than with an endometrial biopsy. The openings of the tubes were located by touch and the cautery was used for three to four minutes. The patient was kept under observation for half an hour and then allowed to return home. Hysterosalpingograms were obtained in six and twelve weeks in most cases.

The results of these studies are summarized in Table I.

Results

Bilateral tubal occlusion as demonstrated by hysterograms was obtained in 23 patients; 15 have been followed for 12 plus months and no pregnancies resulted* (Table I). Three patients became pregnant within six weeks and one of these, delivered recently, now has bilateral tubal occlusion as proved by salpingograms.

There were 14 failures, 9 with unilateral and 5 with bilateral patency. It was interesting to note that if the first coagulation failed to accomplish tubal occlusion subsequent attempts seldom succeeded. Follow-up examination of six to ten months showed that at least 7 of these 14 patients have not become pregnant.

TABLE I.

	Bilateral Occlusion	Failures	Unknown	Total	
No. of patients	23	14	8	45	
Pregnancy	. 8	7	3	18	
Complications	0	0	2	2	

There were 8 women who did not return for salpingograms or further examination. In this group there are 3 known pregnancies.

There were 2 complications, both occurring in the 9 patients mentioned above. One patient developed parametritis and the other developed a venenation to Merthiolate solution.

Comment

The over-all success of less than 50 per cent sterilization in this series is not satisfactory. Hyams does not report his success with his method but reports it as a technique which may be employed. Recent investigators in Japan have followed the Hyams technique on a series of 21 patients. Their results were as follows: of the 21 patients, 7 patients had bilateral tubal occlusion, 5 had unilateral tubal occlusion and the method was unsuccessful in 9 cases. It appears that the use of visual control through the fluoroscope did not greatly enhance the success of the procedure and does greatly complicate it.

The question of the time of the closure of the tube is of some interest. In 2 instances the patient became pregnant within a few weeks of coagulation

^{*}A subsequent resurvey 24 to 36 months later disclosed 5 additional pregnancies.

but on postpartum check the tubes were found to be closed. Apparently a fertilized ovum passed the area of coagulation prior to occlusion.

In one instance the patient was pregnant at the time of coagulation. She had an abortion in two weeks without complications.

It is impossible to state that the tubal occlusion obtained by this procedure is permanent. To date (one year past coagulation) 8 of the 23 women in whom occlusion was successful as demonstrated by hysterosalpingogram have become pregnant.

While the percentage of success is low, this procedure would reduce by half the number of women who require hospitalization for surgical sterilization.

This series of patients was obtained at random without selection. It was noted that in some women there was a slight distortion of the uterine cavity or other factors which made it more difficult to locate the cornua. More critical selection of patients undoubtedly would enhance the percentage of success.

Conclusions

- 1. The modified Hyams technique of transuterine tubal coagulation is simple, easy, and without undue discomfort to the patient and obviates the need for anesthesia and hospitalization.
- 2. In patients selected at random only about 50 per cent obtained tubal occlusion by this technique.
 - 3. This technique does not provide a reliable means of sterilization.

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THE VALUE OF ROUTINE CERVICAL SMEARS IN THE DETECTION OF INCIPIENT CERVICAL CARCINOMA IN PREGNANT WOMEN*

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THE value of routine smears in the detection of incipient carcinoma of the cervix in the nonpregnant woman has been recognized by most gynecologists today, but their value during pregnancy remains controversial.

The reason for this stems from reports in the literature^{4, 8, 10} which indicate that various atypical epithelial hyperplastic changes occur in pregnancy which are reversible, including at one extreme identical cellular atypism characteristic of carcinoma in situ; therefore abnormal smears obtained from these lesions do not indicate actual disease with a sufficient accuracy to warrant its routine use. In fact, many pathologists are reluctant to make a diagnosis of carcinoma in situ during pregnancy even though the cellular atypism would clearly justify the diagnosis were the patient not pregnant.

The purpose of this study is: (1) to determine the efficiency of routine cervical smears in pregnancy for the detection of incipient carcinoma, and (2) to determine whether abnormal smears during pregnancy are indicative of comparable anaplastic lesions or are mostly reversible and thus of limited value.

Our study of routine cervical smears from 5,935 pregnant women appears to shed some light upon this confusing problem. We are in support of the convictions of Hirst and Brown, Carter and co-workers, and Cuyler and associates that routine smears are of real value in the discovery of preinvasive and early incipient invasive carcinoma in the pregnant cervix.

In general we believe definitely abnormal smears, especially Class IV and Class V, remain abnormal until after delivery and will reveal comparable histopathological findings.

Our material shows that most abnormal epithelial hyperplasia such as premalignant dysplasia and carcinoma in situ occurring during pregnancy are not the result of pregnancy. These lesions will remain with the host unless destroyed by biopsy or cautery so that no residual lesion is found by further study.

Material and Method

From July, 1950, through December, 1955, 55,649 cervical smears from 34,920 patients were screened by the Gynob Cytological Laboratory. From

^{*}This study was aided in part by a special project grant No. CS-9428 from the National Cancer Institute, U. S. Public Health Service.

January, 1951, through December, 1955, routine smears were taken by the Gynob Group of obstetricians and gynecologists from 5,935 pregnant women. Whenever possible, repeated smears were taken periodically through the entire pregnancy from patients who manifested initial abnormal smears (Classes III, IV, and V).

In order to evaluate the true nature of the smear, most patients were followed only by repeated cervical smears. Biopsy or cold cone was deferred until at least six weeks post partum. By avoiding biopsies when possible during pregnancy, we attempted to obtain an actual appraisal of whether or not abnormal smears regressed to normal following delivery, and in correlation whether or not the underlying abnormal tissue regressed to normal as has been indicated by several reports in the literature. Piopsies of course were taken on all patients who had clinical evidence of carcinoma or who had Class V smears suggesting invasive carcinoma. Prior to evaluating our final results, all abnormal smears were reappraised in view of our present knowledge. These smears were intermingled with our routine smears without the knowledge of any previous interpretation by the reviewing author. Four of the smears were reclassified. Three were removed from Class IV and revised to Class III. The remaining one was reclassified from Class V to Class III.

Multiple or serial sections were made on all tissues, and the diagnosis was based on the opinions of certified pathologists. Equivocal cases were referred to several pathologists for opinions, and in a few of our cases slides were sent to Emil Novak or Arthur Hertig for final diagnosis.

Results

There were 45 abnormal smears from the 5,935 pregnant women screened. Twenty-two were Class III, 14 were Class IV, and 9 were Class V (Table I). Our classification may be summarized as follows:

- Class I-II: Negative for malignancy.
- Class III: Equivocal—indicates benign atypical hyperplasia or premalignant dysplasia and possibly preinvasive carcinoma.
- Class IV: Probable carcinoma-most often carcinoma in situ.
- Class V: Definite evidence of carcinoma—carcinoma in situ or invasive carcinoma.

In our Class III group of 22 patients, 7 became cytologically negative post partum and tissue study was not done. Six cases had postpartum diagnosis with the following findings: one atypical hyperplasia, 3 premalignant dysplasia, and 2 preinvasive carcinoma. The remaining 9 patients were lost to follow-up, and postpartum study has not been completed.

Of the 14 Class IV smears during pregnancy, 4 cases of premalignant dysplasia, 7 of preinvasive carcinoma, and one of invasive carcinoma were detected. Two of these cases were lost to follow-up studies.

Table I. Survey of Histological Findings and Follow-up in 45 Abnormal Smears Obtained From 5,935 Pregnant Women

			HISTOLOGIC	NO BIOPSIES,			
CLASS	NO. OF			PRE- INVASIVE INVASIVE CARCINOMA CARCINOMA		FOLLOWED WITH NEGATIVE SMEARS ONLY	NO FOLLOW- UP
III	22	1	3	2		7	9
IV	14	0	4	7	1		2
V	9		3	4	2		
Total	45	1	10	13	3	7	11

TABLE II. PATIENTS WITH ABNORMAL SMEARS DURING PREGNANCY AND SUBSEQUENT ABNORMAL TISSUES IN POSTPARTUM PERIOD

NAME	CHARACTER OF SMEARS AND DATES OBTAINED	DATES OF BIOPSIES AND PATHOLOGICAL DIAGNOSIS
B. C.	5/17/52 Smear Class III—2½ months pregnant 11/23/52 Smear Class III—8½ months pregnant	12/1/52 Delivered. Cold knife biopsies of entire squamocolumnar junction immediately post partum. Diagnosis: Potentially malignant dyskaryosis. One year post partum, biopsies and electroconization—atypical hyperplasia
I. A.	1953 Smear Class IV—pregnant 7/26/54 Smear Class IV—post partum	9/2/53 Biopsies while pregnant— chronic cervicitis 7/29/54 Biopsies 5 months post par- tum—premalignant 9/3/54 6 months post partum—cone— preinvasive
V.C.	4/27/53 Smear Class V—4 months pregnant 11/9/53 7 weeks post partum—smear Class V	11/9/53 Biopsies 4 quadrants—chronic cervicitis 11/20/53 Cold cone—preinvasive car- cinoma
В. Н.	1953 Smear Class IV—pregnant 1/26/54 Post partum—smear Class IV	5 months post partum—preinvasive
V. H.	1953 Smear Class IV—pregnant; delivered July, 1953 Returned May, 1954. Postpartum check—smear Class V 12/54 2 months pregnant—smear Class IV	May, 1954 10 months post partum— cold cone—late preinvasive carci- noma with gland involvement. Re- fused hysterectomy 12/21/54 Biopsies during pregnancy— late preinvasive
V. A.	11/9/54 Smear Class III-IV—pregnant 2/21/55 Smear Class III-IV—pregnant 5/23/55 Smear Class III-IV—pregnant	Biopsies 3 months post partum—preinvasive
В. С.	7/12/54 2 months pregnant—smear Class III 2/3/55 Smear Class III—pregnant 2/14/55 Smear Class III—pregnant; 6 weeks post partum—smear Class III	4/21/55 2½ months post partum, 4 quadrant biopsies—preinvasive. Reviewed by another pathologist—premalignant dysplasia. Followed by cone—probable preinvasive
J. K.	10/12/54 Smear Class III—pregnant 10/20/54 Spontaneous abortion 1955 Smear Class V—2 months post partum	14 months post partum—biopsies—pre- invasive
P. O.	3/14/54 Smear Class IV—pregnant 10/29/54 Smear Class IV—pregnant 1/15/55 Smear Class IV—6 weeks post partum	Biopsies 3 months post partum—preinvasive
M. Sc.	1955 Smear Class V—pregnant	Biopsies (8 pieces)—2 months preg- nant—extensive preinvasive 8/23/55 Cold cone 6 weeks post partum —early invasive
M. St.	7/2/54 Smear Class IV—pregnant 12/12/55 Smear Class III—7 months post partum	12/2/54 Pregnant; punch biopsies—chronic cervicitis—cauterized 1/10/56 8 months post partum—early preinvasive
S. F.	3/1/54 3½ months pregnant—smear Class III 5/3/54 5½ months pregnant—smear Class III 6 weeks post partum—smear Class III months post partum—smear Class III- IV	3 months post partum: cold cone—pre- malignant dysplasia

TABLE II-CONT'D

NAME	CHARACTER OF SMEARS AND DATES OBTAINED	DATES OF BIOPSIES AND PATHOLOGICAL DIAGNOSIS Postpartum biopsies—premalignant dys plasia				
V.D.	1954 Smear Class IV—pregnant					
E.S.	1953 Smear Class III—not pregnant; delivered 11/12/53 8/24/54 Pregnant—smear Class III-IV 11/18/54 Delivered 1/15/55 2 months post partum—smear Class III-IV	1/26/55 Wide cold cone—premalignant dysplasia				
L. K.	3/6/53 Smear Class IV—pregnant; de- livered 9/53 2/9/55 Smear Class V	3/2/55 18 months post partum—biopsies and electroconization—premalignant, questionable preinvasive				



Fig. 1.—Patient F. J. (Table III). High-power photomicrograph showing carcinoma in situ during early pregnancy.

Of the 9 patients with Class V smears, 3 had premalignant dysplasia (borderline lesions), 4 had preinvasive carcinoma, and 2 had invasive carcinoma.

The total yield for routine screening of 5,935 pregnant women was 13 preinvasive and one clinically unsuspected early invasive carcinoma. Two additional invasive carcinomas were clinically suspected and thus not credited to our smear detection. Ten cases were diagnosed as premalignant dysplasia and one as atypical hyperplasia.

Table II shows the number of patients with abnormal smears who have been followed during pregnancy mainly by repeated smears and subsequently by biopsies or cold cone in the postpartum period. In 3 of these cases (I. A., V. C., and M. Sc.), it is significant to note that the abnormal smears were

more accurate in indicating the degree of abnormality than the initial punch biopsies. Also of significance is the fact that repeated smears during pregnancy continued to be abnormal up to the date of delivery and in the post-partum period before biopsies were taken.

Table III shows the remaining cases with abnormal histological findings proved by biopsies during pregnancy. A typical example of this group is illustrated by Fig. 1.

TABLE III. PATIENTS WITH ABNORMAL SMEARS AND PROVED ABNORMAL HISTOPATHOLOGICAL FINDINGS DURING PREGNANCY

NAME	CHARACTER OF SMEARS	PATHOLOGICAL DIAGNOSIS
M. L.	Class IV	Biopsy—premalignant; followed by cautery 6 months later—negative smear
K.L.	Class IV	Biopsy—carcinoma in situ. No postpartum follow-up as yet
С. Н.	Class V	Biopsies—preinvasive carcinoma. No follow- up yet
F. J.	Class IV. 7 weeks pregnant	Biopsies—preinvasive carcinoma. Followed by electroconization. Aborted shortly afterward. Followed with negative smears Also had carcinoma of eyelid
М. Н.	Class V. 2 to 3 months pregnant	Biopsies—invasive carcinoma 4/7/53 Threatened abortion 4/10/53 Spontaneous abortion. Curettage followed by Wertheim hysterectomy
A. S.	Class IV. 21/2 months pregnant	Biopsies—invasive carcinoma. Followed by Wertheim hysterectomy
J. P.	Class III B. 7 weeks pregnant	Biopsies—premalignant. Had spontaneous abortion. No follow-up
J.W.	Class III B	Biopsies—carcinoma in situ. No further follow-up
A. M.	Class III B 7 to 8 weeks preg- nant	Cone—carcinoma in situ. Had spontaneous abortion followed by curettage. Fol- low-up—negative smears
J. L.	Class V	Biopsies with cautery to control bleeding— pseudoepitheliomatous dyskaryosis (pre- malignant). Moved to Texas—lost to follow-up
M. F.	Class III A	Biopsies-atypical hyperplasia
B. McC.	Class V	2 punch biopsies—premalignant hyper- plasia. Lost to follow-up

The average age of 5,935 pregnant women was 27 years in comparison with 36 years in 28,965 nonpregnant women screened by our laboratory. The average age of pregnant women who harbored preinvasive carcinoma was 26.9 years in comparison with 36.3 years in the nonpregnant women. The average age of the 3 patients with invasive carcinoma in the pregnant group was 32.6 years.

Table IV illustrates the number of preinvasive carcinomas detected in the various age groups in both pregnant and nonpregnant women. In order to diminish differential bias, all cases with presenting symptoms possibly related to the carcinoma in situ were excluded up to the age of 35. The number of

pregnant women above this age was too few for further comparison. In fact, the greater number of our pregnant patients were between the ages of 20 and 32. Therefore, this group is of most value for comparative study.

TABLE IV. COMPARISON OF NUMBER OF PREINVASIVE CARCINOMAS IN THE VARIOUS AGE GROUPS OF THE PREGNANT AND NONPREGNANT PATIENTS

		PREGNANT		NONPREGNANT*			
		IN SITU	CARCINOMA		IN SITU CARCINOMA		
AGE	NO. EXAMINED	NO.	PER 1,000 EXAMINED	NO. EXAMINED	NO.	PER 1,000 EXAMINEI	
All ages	5,935	13	2.19	28,965	195	6.73	
15-19	•	0	0		2	6.07	
20-24		4	0.67		17	0.59	
25-29		5	0.84		33	1.14	
30-34		4	0.67		46	1.59	
35-39		0			39		
40-44		0			21		
45+		0			37		

*All cases where the in situ lesion could have been responsible for the presenting symptoms to age 35 have been excluded. To avoid differential bias, 7 cases have been excluded from the nonpregnant group because of bleeding.

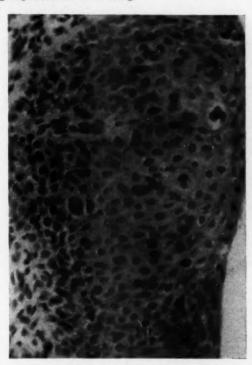


Fig. 2.—Patient S. F. High-power photomicrograph. Premalignant dysplasia showing dyskeratosis with irregular hyperchromatic nuclei and some mitotic figures. Normal stratification in upper few layers is still present.

It is interesting to note that the number of carcinomas in situ detected in the pregnant group in age groups 20-24 and 25-29 (Table IV) is quite similar to the number in the nonpregnant group, indicating that carcinoma in situ may be as prevalent in the pregnant women when equal numbers and various related factors are considered.

This comparison is not to be misconstrued as indicating that carcinoma is more or less prevalent in pregnant women or occurs at an earlier age than

in the nonpregnant women, but is merely to show the comparative ages and findings of the patients in this study with an indication, as has been mentioned, that it may be as prevalent in the pregnant as in the nonpregnant women. A true comparison of statistical value can be made only where large series of each group are carefully analyzed in regard to equal number, age, parity, and other related pertinent factors. This is beyond the scope of this paper.

We hope to have a more definite statistical analysis of a larger group of pregnant women in the next few years.

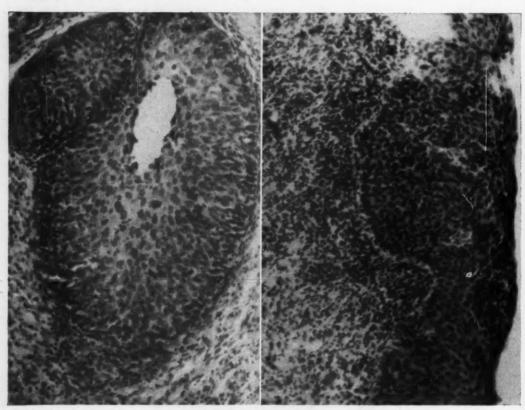


Fig. 3.

Fig. 4.

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b

Fig. 3.—Patient V. H. Photomicrograph of initial biopsies of deep endocervical gland almost completely replaced by neoplastic cells in patient with extensive preinvasive carcinoma detected by cervical smear during pregnancy. Note small circumscribed collections of similar atypical cells probably confined within a gland. Tissues obtained 10 months post partum.

Fig. 4.—Same patient, V. H. Low-power photomicrograph showing residual carcinoma in situ during subsequent pregnancy detected again by cervical smear.

Illustrative Case Reports

Three cases with unusual features are summarized in the following reports:

CASE 1.—S. F., aged 15½ years, gravida i, had a normal cervix. The first cervical smear on March 1, 1954, at 3½ months' pregnancy and a repeat smear at 5½ months' pregnancy were reported as Class III B, compatible with premalignant dysplasia. She was delivered uneventfully on Aug. 18, 1954. A repeat smear 6½ weeks post partum was again Class III B. A repeat smear at 3 months post partum was reported as Class III-IV. Multiple biopsies were taken followed by electroconization. Multiple sections showed

premalignant dysplasia (Fig. 2). On Oct. 29, 1955, the patient returned 4 months pregnant. A repeat smear was negative and the cervix normal. The delivery of the second child on April 20, 1956, was uneventful.

Comment.—The persistence of abnormal smears during pregnancy and in the post-partum period which led to the detection of a premalignant or borderline lesion in a 15½-year-old primipara is of special interest.

CASE 2.—V. H., aged 28 years, was a multipara. In 1953 while pregnant, a routine smear was reported as Class IV. The cervix appeared normal. Uneventful delivery occurred in July, 1953. The patient did not return until May, 1954, about 10 months post partum. A repeat smear at this time was Class V. Sharp knife conization followed by electroconization was done in June, 1954. The diagnosis was late preinvasive carcinoma of the cervix with extension deep into the endocervical glands (Fig. 3). The patient refused operation. She returned in August, 1954, when the cervix appeared normal. A repeat smear was Class

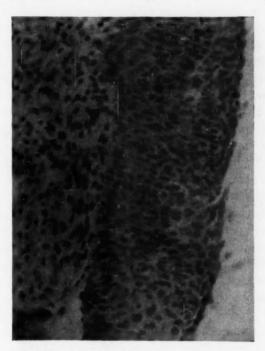


Fig. 5.—Patient M. Sc. Photomicrograph of one area of carcinoma in situ extending up endocervical canal.

III B. The patient did not return until December, 1954, at which time she was 2 months pregnant. A repeat cervical smear was Class IV, suggesting preinvasive carcinoma. On Dec. 21, 1954, multiple biopsies were done, followed by extensive cauterization. The diagnosis again was preinvasive carcinoma (Fig. 4). February, 1955, a repeat smear was negative. At term a repeat smear was negative. She was delivered in July, 1955, uneventfully. Two months post partum the repeat smear was negative and the cervix normal. The patient is being followed. She refused hysterectomy.

Comment.—The abnormal smear obtained during the first pregnancy detected carcinoma in situ which was diagnosed about ten months post partum. A repeat smear taken during the second pregnancy again detected residual carcinoma in situ which was apparently destroyed by biopsies and subsequent cautery.

Case 3.—M. Sc., was 27 years of age. On July 2, 1954, when she was 2 to 3 months pregnant, a Class IV smear was obtained, suggesting preinvasive carcinoma. She then moved

to San Francisco, where follow-up punch biopsies showed only chronic cervicitis, no malignancy. Following delivery a small erosion of the cervix was cauterized. She returned to San Diego on Dec. 12, 1955, about 8 months post partum. A repeat smear was reported as Class III. Follow-up multiple biopsies showed an equivocal carcinoma in situ. Representative sections were sent to Dr. Emil Novak, who confirmed the diagnosis of carcinoma in situ (Fig. 5).

Comment.—In this case the original cervical smear during pregnancy was more accurate than subsequent punch biopsies which gave a false sense of security, and only through a repeat abnormal smear was the actual lesion detected.

Comments

Are routine cervical Papanicolaou smears in pregnant women indicated in private practice? Our findings indicate that they will detect unsuspected cancer probably as frequently as routine smears in the nonpregnant patients of comparable age when related or contributing factors are equally considered. Of course the over-all percentage of detection will be lower since pregnant patients form a younger age group than nonpregnant. The detection of 13 unsuspected preinvasive and one unsuspected invasive carcinoma among 5,935 patients seems impressive. Probably the one incipient invasive carcinoma would have gone unrecognized without the use of the smear.

The evidence obtained from our study thus far strongly indicates that definite abnormal smears (Class IV and Class V) will remain practically the same in the postpartum period and will reveal abnormal or atypical histological findings comparable with the smear with a high degree of accuracy (Table II). Our three case reports especially exemplify this point.

This study further indicates, as has been mentioned in the introduction, that abnormal lesions of the cervix during pregnancy, such as premalignant dysplasia and preinvasive carcinoma, are definite pathological changes and will persist with the host if not removed by multiple biopsies or treated during pregnancy. On this point our investigation seems to substantiate the work of Carrow and Greene, and of Peckham, Greene, and associates.

The fact that 7 cases out of 22 Class III smears reverted to negative after delivery requires some comment. As has been mentioned, we consider our Class III equivocal, indicating various degrees of atypical hyperplasia or premalignant dysplasia and possibly preinvasive carcinoma. Lesions underlying these Class III smears may have been basal-cell hyperplasia which was reversible or some atypical dysplasia which reverted to normal, or our interpretation was false. We are continuing to study this group for better evaluation.

An abnormal smear during pregnancy seems to be more accurate than one or two punch biopsies taken at random. This is exemplified in 3 of our cases in which biopsies during pregnancy showed only chronic cervicitis, whereas more complete biopsies or cold cone in the postpartum period showed definite preinvasive carcinoma.

It has been our observation from this study that a pregnant patient with a normal-appearing cervix from which a Class III smear is obtained may safely be followed into the postpartum period before definitive diagnosis and treatment are carried out. One may speculate that a patient with a Class IV smear, suggesting a preinvasive carcinoma from a normal-appearing cervix, may also be followed with only repeated smears until the postpartum period. However, all cervices showing a lesion grossly suspicious of malignancy or with a Class V smear should definitely be biopsied to rule out invasive carcinoma.

Conclusions

Our study indicates that routine cervical smears in pregnancy are of definite value in detecting preinvasive and incipient invasive carcinoma as well as premalignant lesions. This is based on a study of routine smears from 5,935 pregnant women. Definite abnormal smears obtained during pregnancy usually remain abnormal and are indicative of comparable atypical lesions ranging from atypical hyperplasia to invasive carcinoma.

Grateful acknowledgment is made to Dr. James E. Sandell for the preparation of the photomicrographs for this study, and to Dr. John Dunn, Jr., Field Investigations and Demonstrations Branch, National Cancer Institute, for his review and constructive criticism of this paper.

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2107 FIFTH AVENUE

PRECLINICAL CARCINOMA OF THE CERVIX

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As a result of our experience over the past ten years^{1, 2, 6} with methods of detection and diagnosis of early cancer of the cervix, we have now accumulated a series of cases which permits some observations on the nature of this pathological process and its treatment. We feel at the present time, and agree with Harris and Peterson,⁴ that the only basis for consideration of this problem must be carefully performed ring biopsy or cold knife conization, with step-sectioning of serial blocks of the biopsy, together with endocervical curettage. This contention is amply borne out by Fig. 4, which shows that prior to the establishment in 1950 of a consistent program of ring biopsy and endocervical curettage on all patients with positive cytology and clinically negative cervices, very few preclinical cancers were diagnosed.

Since the establishment of extensive cytological screening in this clinic in 1947, with routine ring biopsy and endocervical curettage in cases with positive cytology and no clinical lesion, it has become apparent that many cancers of the cervix can be detected by these means before any clinical evidence or manifestations have developed. These have been termed preclinical cancers, which is usually interpreted to mean carcinoma in situ. We have been impressed, however, by the fact that we have encountered a certain number of preclinical cancers which have been more extensive than carcinoma in situ, in that they have shown questionable or minimal invasion of the stroma (beyond endocervical gland penetration which we consider to be consistent with carcinoma in situ) as is demonstrated in Fig. 1, yet the cervix is completely normal clinically. This penetration is microscopic, localized to the immediate area of breakthrough of the basement membrane, does not extend diffusely into the stroma, and does not show evidence of lymphatic involvement. The photomicrograph in Fig. 2 illustrates such an area of early stromal invasion. However, we do not include in this group cases in which there is a normalappearing portio with well-established invasion of the stroma of the endocervix, as is demonstrated in Fig. 3.

Because this group is difficult to define, and is not included in the International Classification, we have used the term "early invasive" to categorize these cases, and have inserted them, in our own records, between Stage 0 and

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Stage I. This is similar to the group referred to by Wheeler and Hertig⁸ as "clinically unsuspected carcinoma of the cervix." We have isolated this group for special study, because a large proportion of early cervix cancer

Fig. 1.

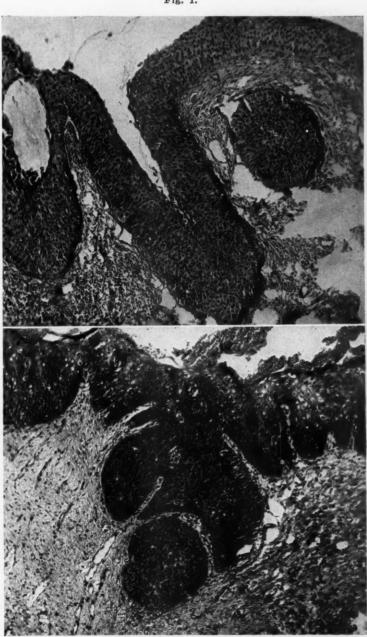


Fig. 2.

Fig. 1.—Photomicrograph showing typical carcinoma in situ with endocervical gland involvement. We consider this to be noninvasive.

Fig. 2.—Photomicrograph showing surface carcinoma in situ with early invasion of the subjacent stroma.

picked up by cytological screening will be found to lie in this stage. In fact, more than half of our series of preclinical cancers can be included in this group. Therefore knowledge of its clinical behavior and response to treatment is of paramount importance.

At the present time, on the basis of an average annual total of 8,000 routine cytological screenings, we find approximately half of all our cervix cancers in the preclinical group (Table I). There is no doubt that if we could double the number of cytological examinations, the number of preclinical cancers of the cervix would rise proportionately.

TABLE I, INCIDENCE OF PRECLINICAL VERSUS CLINICAL CANCER OF THE CERVIX

	1947	1948	1949	1950	1951	1952	1953	1954	1955
Preclinical	2	0	1	18	19	26	30	32	24
Clinical	38	42	29	34	27	25	28	35	27
Total cytology	1,110	1,320	3,457	4,671	5,598	7,251	7,261	7,383	8,274
% preclinical	5	0	3.3	34.6	41.3	50.9	51.7	47.7	47.0



Fig. 3.—Photomicrograph showing normal portio epithelium with invasive carcinoma arising from the endocervical canal. Although clinically negative, this lesion is readily detected by endocervical curettage and ring biopsy. This type of case is not included in the preclinical early invasive groups.

From Jan. 1, 1947, to Dec. 30, 1955, there were 154 cases of preclinical cancer diagnosed at the Royal Victoria Hospital by ring biopsy with endocervical curettage and step-sectioning of serial blocks of the biopsy.⁵ These were the result of cytological screening of clinically negative cervices. Of

these, 57 were classified as carcinoma in situ and 97 were classified as "early invasive." The relation of preclinical cancer to clinical Stage I is shown in Fig. 4.

It should be noted that the institution in 1950 of routine ring biopsy and endocervical curettage of all clinically negative cervices with positive cytology resulted in a great increase in detection of preclinical cancers without a proportionate increase in the number of cases screened. In other words, without such total biopsy procedures, many preclinical cancers had escaped detection and were classified as cytological false positives by the usual punch biopsy.

Table I shows the incidence of preclinical and clinical cancer of the cervix in our clinic together with the total cytology screenings. A sharp rise in preclinical lesions appears in 1950 with the adoption of routine ring biopsy of clinically negative cervices, and continues to parallel the increasing cytology totals. It is to be noted that this is a net increase, and is not at the expense of clinical lesions.

For the purpose of this study, we have separated the "early invasives" from the remainder of Stage I because we feel that they represent an intermediate group falling between carcinoma in situ and clinical cancer restricted to the cervix. With this in mind, we have examined the age incidence for all stages of cancer of the cervix. The results are shown in Table II.

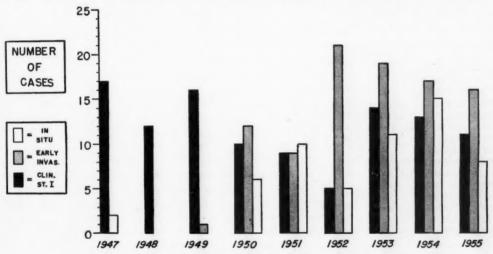


Fig. 4.—Preclinical and early clinical cancer of the cervix.

TABLE II. AGE INCIDENCE OF CANCER OF THE CERVIX, ROYAL VICTORIA HOSPITAL

STAGE	MEDIAN (YEARS)	MEAN (YEARS)	MODE (YEARS)
0	34.0	35.8	30-34
Early invasive	35.7	38.1	35-39
I (clinical)	48.0	47.5	50-54
II '	51.0	51.1	50-54
III	52.0	52.5	45-49
IV	58.0	55.8	60-64

We note a gradual increase in the age of incidence in these progressive stages of cancer. This same progression was noted by Wheeler and Hertig,⁸ although their actual ages of incidence were a few years higher than ours

for all stages of the disease. Examination of modal numbers, however, which represent the age of greatest incidence, shows these to be the same in both series. There is an indication, from examination of our modal numbers, that the time interval between the carcinoma in situ, "early invasive," and clinical Stage I, appears to be longer than the interval indicated by the average ages of incidence, and conforms with several other reports in the literature^{3, 7, 9} of the prolonged interval possible between preclinical and clinical cancer.

This is one of the factors which reassures us in observing, without treatment, preclinical cancer in young women who are desirous of subsequent children. This attitude, of course, is predicated on the availability of excellent cytological and follow-up facilities, permitting at least semiannual cytological examination.

From the clinical viewpoint, it is interesting to note that of the 57 patients with carcinoma in situ, 14, or 24.5 per cent, complained of abnormal bleeding, whereas in the "early invasive" group, 38, or 39.1 per cent, complained of abnormal bleeding. We feel that this increased bleeding tendency of the "early invasive" group occupies an intermediate place between the incidence of bleeding in carcinoma in situ and in clinical cancer, and may represent further support for considering this as a separate, intermediate group.

During the period of observation of this series, our attitude has changed progressively toward conservatism in treatment. Our methods of treatment are shown in Table III.

TABLE III. TREATMENT

TREATMENT	CARCINOMA IN SITU	EARLY INVASIVE
Half standard radium	1	4
Standard radium	0	28
Standard radium, x-ray	0	9
Half standard radium, hysterectomy	0	3
Half standard radium, hysterectomy, B.S.O.	2	12
Standard radium, hysterectomy, B.S.O.	0	3
Standard radium, hysterectomy, x-ray	0	1
Hysterectomy	26	16
Hysterectomy, x-ray	0	1
Hysterectomy, B.S.O.	11	11
Wertheim hysterectomy	0	3
Hysterectomy, B.S.O., x-ray	0	1
Amputation of cervix	0	1
X-ray only	0	1
Ring biopsy, curettage of endocervix only	17	3
Total	57	97

On critical evaluation of these various methods of treatment, it is obvious that we have vacillated, for one reason or another, between extremely radical treatment in some cases and no treatment beyond ring biopsy in others. This diversity of treatment is in keeping with that in similar series reported, and demonstrates our uncertainty as to the treatment of choice over this period of time.

Results

Of the 57 patients who had carcinoma in situ, all are known to be alive and well. Of the 17 who received no definite treatment beyond ring biopsy, 16 have remained cytologically negative to date. One patient, aged 77 years, has recently had recurrence of positive cytology in a clinically negative cervix 3 years after ring biopsy. As this patient also suffers from

primary breast cancer of recent origin, it is unlikely that further gynecological surgery will be contemplated. Four patients in this group have had subsequent pregnancies.

Of the 97 patients with "early invasive" cancer, 96 are known to be alive and well; 3 of these received no treatment beyond ring biopsy and endocervical curettage. One patient died of proved syphilitic heart disease one year after treatment, with no evidence of recurrence.

Thus we can conclude that of the 154 patients under study, 153 are known to be alive without evidence of recurrence after a period of observation of from 6 months to 9 years. Of these 153 patients, 40 have been observed 5 years or more.

Thus we may be justified in concluding from this preliminary survey that all the previously mentioned forms of treatment are equally successful in the management of preclinical carcinoma of the cervix. It is interesting and important to look at this series from the point of view of complications of treatment. We find that 2 of the 3 patients treated by Wertheim hysterectomy developed ureteral fistulas necessitating nephrectomy. Of the group treated radiologically, 2 patients developed extensive radiation necrosis necessitating abdominoperineal resection, in spite of the fact that they received only 3,000 mg. hr. of radium to the cervix, which is half our standard dose. One of these patients had carcinoma in situ, the other had "early invasive" cancer. As a result of these serious complications, and the lack of evidence of recurrence in the series as a whole, we have become increasingly encouraged to attempt to determine the minimal effective treatment for preclinical cancer of the cervix. At the present time, we feel that total hysterectomy with removal of a 1 to 2 em. vaginal cuff is an adequate form of definitive treatment.

Furthermore, we strongly advocate a conservative approach in young women with carcinoma in situ who are desirous of further pregnancies, provided they fully understand the implications and are willing to present themselves for continual cytological follow-up. We are not as yet in a position to recommend this conservative attitude in cases of "early invasive" cancer, but are willing to consider it in exceptional cases.

Although we do not have an adequate number of cases with 5 year followup, it is fairly evident that the results of treatment of "early invasive" cancer of the cervix by the methods described are comparable to those attained for carcinoma in situ, which are considerably better than the results for clinical Stage I. The intermediate position of the age incidence of "early invasive" cancer, its intermediate position from the point of view of abnormal bleeding, and its high survival rate clearly justify the segregation of these cases in a separate category. We urge that this group of cases be separated, identified, and studied, because it is a group which can be treated very successfully by relatively conservative means.

This group is apparently closer in its age incidence and response to treatment to International Stage 0 than to Stage I, yet International Stage 0 by definition cannot be made to include this group of cases. On the other hand, since Stage I is a clinical stage, and since these cases cannot be detected by clinical examination, their continued inclusion in Stage I is equally unjustified. The inclusion of "early invasive" cancer of the cervix can confuse the results obtained in the treatment of Stage I lesions by any given method. Obviously, when 50 per cent or more of the Stage I cases are "early invasive" (as in our experience), and thus fall in a group which we have demonstrated to be virtually 100 per cent curable by simple methods, a false sense of achievement may arise from the application of a new or modified form of treatment to Stage I when it includes this group, when in all probability the success of

such treatment for clinical lesions is no greater than that attained by standard methods. It is very likely that the wide dicrepancy in the results claimed in treatment of Stage I lesions can be explained on this basis, and this should be borne in mind when an evaluation of various modes of treatment is made.

The solution appears to be either the creation of a new stage designation, or a subdivision of either Stage 0 or Stage I to include this group, and thus to remove the influence of the inclusion of "early invasive" cases on the results of treatment of Stage I.

Conclusions

1. Extensive cytological examination of the cervix has uncovered a large volume of preclinical cancer.

2. Theoretical considerations can be based only on universal and adequate ring biopsy or cervical conization procedures and endocervical curettage, together with complete and perpetual follow-up. There are many pitfalls in the solution of this problem, and the difficulties are compounded by conclusions drawn from observations on single or quadrant biopsies, or on conizations without endocervical curettage.

3. The large number of preclinical cancers detectable by those methods poses new and interesting clinical problems.

4. There is evidence to support the contention that preclinical cancer should be subdivided into two groups, namely, carcinoma in situ and "early invasive," since the latter group does not satisfy the definition of either Stage 0 or Stage I of the International Classification.

5. The successful treatment of preclinical cancer of the cervix can be carried out by a variety of methods.

6. Carcinoma in situ can be safely and successfully observed only after the minimal treatment which is incidental to ring biopsy or conization plus endocervical curettage. The conservative attitude is frequently rewarded by subsequent pregnancies.

7. The dangers of overtreatment appear to be more serious than the theoretical dangers of conservative methods.

8. Total hysterectomy with removal of the vaginal cuff, and with preservation of the ovaries, appears to be adequate treatment for both carcinoma in situ and "early invasive" carcinoma of the cervix.

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FACTORS THAT MIGHT INFLUENCE PROGNOSIS IN MALIGNANCIES OF THE VULVA*†

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HOUGH this series is relatively small, its value lies in the fact that every A case of malignancy of the vulva observed on the Tulane Unit at Charity Hospital since Jan. 1, 1956, has been cared for in detail by one team assigned to the study of this entity.

From Jan. 1, 1946, through Dec. 31, 1955, 37 cases of invasive malignancy were treated on the Tulane Unit at Charity Hospital, and 10 additional cases were treated by members of the team in private practice. Therefore, a total of 47 invasive malignancies of the vulva were available for study.

In all instances the rigid diagnostic survey which we previously described was performed.1-4 In dealing with invasive malignancies of the vulva, extensive (radical) vulvectomy was performed, with bilateral pelvic extraperitoneal node dissection, consisting of the removal of femoral, superficial, and deep inguinal, Cloquet's, hypogastric, obturator, external and common iliac, and lower aortic and vena caval nodes. In addition, in some cases where the malignancy involved contiguous structures, the operation was extended up to and including total pelvic viscerectomies in an attempt to effect cure.

At the time of operation the regional nodes, as removed, were placed in separate containers in order that, if metastases were encountered, the nodes to which metastasis had occurred could be accurately established.

The distribution of regional nodes with metastasis and the number of cases involved are shown in Fig. 1. It should be observed that metastasis from malignancies of the vulva has been found in the series in each area of regional nodes described and on both the right and left sides.

It is impossible to tell whether or not nodes are involved in the malignant process by palpatory determination of size, consistency, mobility, or fixation of the nodes. In none of these cases did these signs give us an index as to whether or not metastatic tumor would be found in the nodes. Large fixed nodes may show inflammatory reaction, while very small, freely movable nodes have shown malignant involvement.

^{*}Aided by a grant from the Ex-Residents and Fellows Research Fund.

[†]Presented at a meeting of The New Orleans Gynecological and Obstetrical Society on Oct. 16, 1956.

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Therefore, we cannot agree with those who manage malignancies of the vulva and fail to perform pelvic node dissection because nodes are not palpable or, if palpable, do not feel "abnormal." The only way that one can tell whether or not metastasis is present is by histologic sections of the removed tissues.

Of these 47 cases of invasive malignancies of the vulva, 3 patients refused pelvic node dissection following vulvectomy; 2 deserted the hospital following biopsy confirmation of the clinical diagnosis; and 5 cases were judged inoperable due to bone or lung metastasis or such extensive intra-abdominal spread that even the possibility of total pelvic viscerectomy could not be entertained. Thus, in 37 cases, regional nodes were available for study along with the entire vulvar specimen.

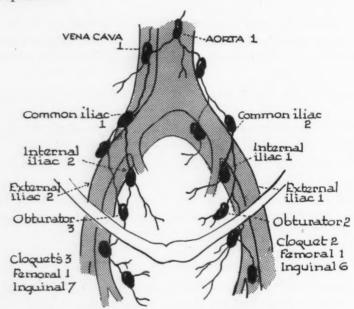


Fig. 1.—Distribution of metastases in the regional nodes.

As previously stated, the nodes from each anatomic region were placed in separate containers and studies of the regional nodes showed metastasis to be present in 11 of the 37 cases, or 30 per cent (Table I).

TABLE I

	CASES	PER CENT
Metases in nodes	11	30
No metastases in nodes	26	70

The location and size of the lesions in patients who showed metastasis to regional nodes are listed in Table II. Every type of possible metastasis occurred. In some, the metastasis was on the ipsilateral side; in others, metastasis was found to be present on both sides. This certainly is an argument against vulvectomy with unilateral node dissection as treatment for malignancies of the vulva, the node dissection being performed on the side on which

the lesion was present, and bears out our contention that when one is dealing with malignancies of the vulva all regional nodes, deep as well as superficial, should be removed. Furthermore, Case 7 (E. L.) had direct metastases to both right and left obturator nodes, whereas all other nodes were free of metastasis. We wish to emphasize the fact that in this case no superficial nodes were found to contain metastasis.

Stanley Way⁵ has suggested the use of a rapid node-smear technique as a means of determining the extent of metastasis. Such means would modify the surgical dissection if no positive nodes were noted. By this method the lowest external iliac nodes are excised and cut, and a smear is made and stained. If it is negative for metastasis, the inguinal ligament is not divided, and further dissection of the iliac or other deep nodes is not attempted. This idea suggests a continuity of metastasis from the vulva to the superficial and deep inguinal nodes and thence to the iliac, obturator, caval, and aortic nodes. Case 7 (E. L.), cited previously, with direct extension to the obturator nodes, refutes this theory and supports the argument for deep as well as superficial pelvic node dissection when dealing with malignancies of the vulva.

In one instance, Case 1 (L. B.), positive metastatic nodes were found in all of the regional node groups removed. This patient is alive and well 9 years postoperatively.

Size of the Lesion and Lymph Node Metastasis.—In an attempt to correlate the size of the primary lesion with occurrence of positive lymph node metastases, lesions of 1.0, 2.0, 3.0, 4.0, and 5.0 cm. and over were plotted against node metastases occurring with each of the various-sized lesions. Studies of those findings in this series led to a decision that a lesion 3.0 cm. or less in greatest diameter offered less chance of node metastasis and a greater chance of survival than lesions larger than 3.0 cm. in diameter. Perhaps it is an obvious conclusion that, in general, smaller lesions should give a better prognosis. This is true in this series, and, in an attempt to develop a yardstick of various components, it was thought that an exact definition of the size of the lesion which would offer favorable prognosis would be better than just a general statement that the larger lesions are more likely to be accompanied by regional metastases (Table III).

The smallest lesion in this series which showed nodal metastases measured 2.5 cm. in its greatest diameter. The largest lesion, resected and found to be free of regional node metastases, measured 11 by 13 cm. This patient is alive and well after 5 years. From the data derived from Table III, we deduce that with a lesion of the vulva 3.0 cm. or less in diameter one can expect metastatic involvement in 1 out of 7 cases, or 14 per cent; whereas, if the lesion is over 3.0 cm. in diameter, then metastatic node involvement can be expected in more than 1 of every 3 such cases seen, or 39 per cent. Furthermore, in none of the patients who had lesions 3.0 cm. or less in diameter were bilateral metastatic nodes encountered, whereas in 23 patients with lesions over 3.0 cm. in diameter 9 showed metastases (39 per cent) of which 5 were bilateral (56 per cent) (Table IV). In no case, regardless of size, were there contralateral metastases only.

These observations obviously are not statistically significant because of the small number of cases here reported, nor will they serve as a basis on which to vary the operative treatment of the extent previously stated. But they are points on which our interest will remain centered in succeeding cases.

Histologic Grading.—No correlation could be found between the histologic grade of the malignancy and either the presence of metastases or survival (Table V).

	RESULT	No evidence of recur-	No evidence of recur-	rence e- Died 1951	Died 1953	Died 1954	n- Died 1953	n- Died 1954	Died 1949	Died 1955	Died 1952	, Died 1951
OTHER	PROCEDURE	None	None	Excision of recurrence in left inguinal	region None	None	Posterior exen-	Posterior exenteration	None	Vaginectomy and removal of left levator	muscle None	Vaginectomy, excision of right levator muscle
YEAR	TREATED	1947	1948	1951	1952	1953	1953	1953	1948	1954	1952	1949
NODES	LEFT	All	Inguinal	Inguinal	Inguinal	Inguinal	ı	Obturator	ı	1		Inguinal, common iliae, Clo-
METASTATIC NODES	RIGHT	All	1	ı	Inguinal	Inguinal	Inguinal	Obturator	Inguinal Cloquet	Inguinal	Inguinal	External iliac, hypogastric, ob- turator, Cloquet
	GRADE	60	ಣ	63	ಣ	c 1	63	63	ಣ	1	L	က
	TYPE	Squamous	Squamous	Squamous	Squamous	Squamous	Squamous	Squamous	Adenocar-	Adenocar- cinoma	Melanoma	Transi- tional cell
SIZE	(CM.)	5.0	4.0	2.5	5.5	10-	3.0	10-	8.0	4.0	4.0	7.0
LOCATION OF	LESION	Clitoris	White Left labium majus	Negro Left labium majus	Right labium ma-	Left labium majus	Anus and posterior	Both labium majus and minus	and anus Right Bartholin	gland Left Bartholin gland	-	and majus Urethra and va- gina
	RACE	White	White	Negro	Negro	White	Negro	Negro	White	Negro	Negro	Negro
	AGE	35	48	70	28	61	81	89	54	29	75	43
	PATIENT	1. L.B.	2. R. A.	3. R. J.	4. L. S.	5. L. L.	6. A. V.	7. E.L.	8. J. L.	9. G.P.	10. A. M.	11. C.B.

TABLE III. METASTASES IN CASES OPERATED UPON

SIZE OF PRIMARY LESION	NUMBER	WITH METAS- TASIS	WITHOUT METASTASIS	PER CENT	
1-3 cm.	14 cases	2 cases	12 cases	14	
Over 3 cm.	23 cases	9 cases	14 cases	39	

TABLE IV. CASES OPERATED UPON-POSITIVE NODES

SIZE	NUMBER	UNILATERAL	BILATERAL	PER CENT BILATERAL
1-3 cm.	2	2 cases	0 cases	0
Over 3 cm.	9	4 cases	5 cases	56

TABLE V

	CASES OPER	RATED UPON	CASES WITH METASTASES		
GRADE	CASES	PER CENT	CASES	PER CENT	
Not graded	8	22	2	18	
Grade I	1	2.5	0	0	
Grade II	17	46	4	36	
Grade III	10	27	5	46	
Grade IV	1	2.5	0	0	
Total	37	100	11	100	

Type of Lesions Encountered.—Over 80 per cent of the lesions in this series were epidermoid carcinoma (Table VI). The prognosis in this series seems to be best if the patient has epidermoid carcinoma as compared to the miscellaneous group. Of the 37 cases operated upon, 31 had epidermoid carcinoma, and 71 per cent of these patients are alive. Of the 6 cases in the miscellaneous group, one patient, or 17 per cent, is alive.

TABLE VI. TYPE MALIGNANCY

		ALL	CASI	ES		CASES OPER	RATE	D UPON	
TYPE OF MALIGNANT LESION		NUMBER	ALIVE		NUMBER			ALIVE	
Squamous cell		38 (81%)		23 (60%)		31 (84%)		22 (71%)	
Fibrosarcoma	1		1		1		1		
Malignant melanoma	2		0		1		0		
Adenocarcinoma of Barth- olin gland	2		0		2		0		
Transitional cell carcinoma	1		0		1		0		
Melanosarcoma	1		1	*	0		0		
Myxosarcoma	1		0		1		0		
Carcinoma of skin ap- pendage	1		1		0		0		
Subtotal		9 (19%)		3 (33%)		6 (16%)		1 (17%)	
Total		47 (100%)		26 (56%)		37 (100%)		23 (62%)	

Survival

Extensive (radical) vulvectomy and bilateral inguinal and deep pelvic lymph node dissections were recommended for all patients in whom the diagnosis of invasive malignancy of the vulva was made. The only contraindication to operation was the presence of bone or lung or other distant metastasis. No patient was refused surgical therapy because of concurrent medical disease, age, or size of the lesion. The diagnosis of invasive malignancy of the vulva was made in 47 cases. Seven patients were considered to have inoperable cases or deserted prior to definitive therapy. None of these has survived

longer than 18 months. Three patients had extensive vulvectomies but refused further surgery. All of these patients are alive and well. Of the 37 patients treated by vulvectomy and node dissection, 23, or 62 per cent, are living and 14, or 38 per cent, have succumbed to their malignancy or are dead from other causes.

Size of the Lesion in Relation to Survival.—Of 37 patients treated surgically, 14 patients had lesions 3.0 cm. or less in greatest diameter. Ten of these 14, or 71 per cent, are alive. Twenty-three patients had lesions over 3.0 cm. in diameter, and 13, or 56 per cent, of these patients are alive (Table VII).

TABLE VII. SIZE OF LESION AND SURVIVAL—ALL CASES

SIZE	ALIVE	DEAD	PER CENT SURVIVAL
1-3 cm.	10	4	71
Over 3 cm.	13	10	56
Total	23	14	62

Thirty-one patients have been followed over 5 years since surgery. Nineteen, or 61 per cent, are alive, and 12, or 39 per cent, are dead. The correlation of survival with the size of the lesion is again apparent from Table VIII. Our correlated results are in agreement with those of Taussig.⁶⁻⁸

TABLE VIII. CASES ELIGIBLE FOR FIVE-YEAR FOLLOW-UP

SIZE	ALIVE	DEAD	PER CENT SURVIVAL
1-3 cm.	9	3	66
Over 3 cm.	10	9	53
Total	19	12	61

Summary and Conclusions

- 1. Forty-seven cases of invasive malignancies of the vulva were managed between Jan. 1, 1946, and Dec. 31, 1955. Thirty-seven cases were treated by extensive (radical) vulvectomy and bilateral, superficial, and deep pelvic node dissection.
- 2. All cases were studied in relation to size, type of malignancy, grade of the tumor, and survival. Regional node metastases were plotted in those cases in which metastases were present.
- 3. The probability of node metastases and the prognosis for survival have been correlated with the size of the lesion.
- 4. The prognosis for survival is relatively poor if node metastases are present.
- 5. The grade of the tumor, the cellular type, and the location of the lesion do not aid in predicting which patients will have metastases to the regional nodes.
- 6. The inguinal nodes are the most frequent site of regional node metastasis. There is, however, no constant continuity of metastasis from one group of nodes to another.
- 7. Smaller lesions tend to have unilateral metastases if any. Metastases from the larger lesions are more frequently bilateral.

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- 8. The over-all survival for the entire series of 47 cases of invasive malignancy was found to be 55 per cent. Of the 37 cases operated upon, 62 per cent are alive.
- 9. Of the 37 patients operated upon, 11 were found to have regional node metastases. Though this is a small number and not statistically significant, we have plotted the metastases found and compared them to the size of the primary lesion. The following conclusions were reached:
- A. If the primary lesion is 3.0 cm. or less in greatest diameter, one can expect regional node metastases in approximately 14 per cent of the cases. With lesions over 3.0 cm. in greatest diameter, one can expect regional metastases in approximately 39 per cent of the cases.
- B. If the primary lesion is 3.0 cm. or less in greatest diameter, bilateral node metastases will probably not be found; whereas in lesions over 3.0 cm. in diameter, one can expect bilateral node metastases in approximately 56 per cent of the cases.

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URETEROILEOSIGMOIDOSTOMY*

I. A Preliminary Report

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THE importance of a safe and satisfactory means of diverting the urinary stream from the urinary bladder and urethra has grown with the recent advances in radical cancer surgery, especially with the development of radical surgery for pelvic tumors. The use of cutaneous ureterostomy and of "ileal bladder" as a means of diverting the urine has not been entirely satisfactory practice. In addition, there have been instances of obstruction and infection of the upper urinary tract, as well as electrolyte imbalance, following these types of urinary diversion operations, just as there are following ureterointestinal transplantations.

An ideal urinary transplantation operation would have the following features: (a) a low surgical mortality rate; (b) a convenient means of urine disposal in the postoperative period; (c) absence or low incidence of both ureteral obstruction and ascending pyelonephritis; (d) absence of electrolyte imbalance (example, hyperchloremic acidosis with or without azotemia); (e) no features which would require compromise of the extent of radical surgery for malignant disease in order to make possible the transplantation procedure itself.

There has been a progressive improvement in the results following urinary diversion operations over a period of many years. The initial operations of Maydl¹ and Bergenheim² in 1894 left much to be desired. The techniques of Coffey,³ which provided a means of ureterointestinal connection with the sigmoid colon, were fraught with difficulties in categories (c) and (d). The advent of end-to-side anastomosis as described by Cordonnier⁴ has greatly reduced the incidence of obstruction which resulted from Coffey-type operations. Our recent employment of Cordonnier transplants of the end-to-side ureterosigmoidostomy type in more than 100 cases in the Francis Delafield Hospital has convinced us that ascending pyelonephritis still results as either an early or a late sequel to the procedure. We have sought therefore a better means of providing relative asepsis of the upper urinary tract, absence of obstruction and—with these two features—an improvement in the total prognosis for the patient. We have had a limited experience with ileal segments

^{*}This study was supported in part by an institutional grant from the American Cancer Society to Columbia University.

which joined with ureters within the abdomen to the surface of the skin. However, the difficulties associated with this operation and the subsequent complications have been adequately described by Cordonnier,5 who has used the ingenious technique originally described by Bricker.6

Goodwin and Hudson' have described an improved type of Maydl operation in which a "button" of trigonal musculature and epithelial surface is implanted—along with its attached blood and nerve supply—into the rectum or rectosigmoid. This type of operation is obviously not suitable in instances in which radical pelvic excisional surgery must be done in order to eradicate malignancy. These procedures are illustrated in Fig. 1.

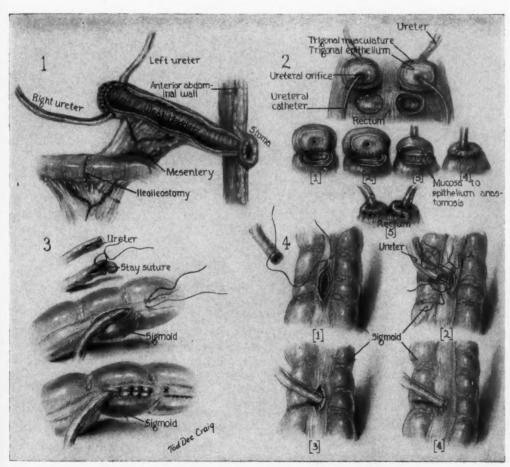


Fig 1.—1, The most recently developed technique (Bricker) utilizing an isolated segment of ileum as a "bladder" which has the ostium located on the anterior abdominal wall. Note the primary ileolleostomy performed to re-establish continuity of the bowel.

2, Technique of implantation of trigonal "buttons" containing an intact ureterovesical valve. Note that this technique requires invasion of the bladder and preservation of the entire ureter on both sides.

3, Early technique of ureterosigmoidostomy (Coffey). In this operation a careful construction of an ostium at the ureterointestinal juncture is not performed.

4, Modern version of the ureterosigmoidostomy which has been widely employed (Cordonnier). Note that there is an outside row of sutures beginning in [1] and an inside row of absorbable sutures shown in [2] and [3]. The anastomosis is completed by the anterior row of interrupted silk sutures shown in [4].

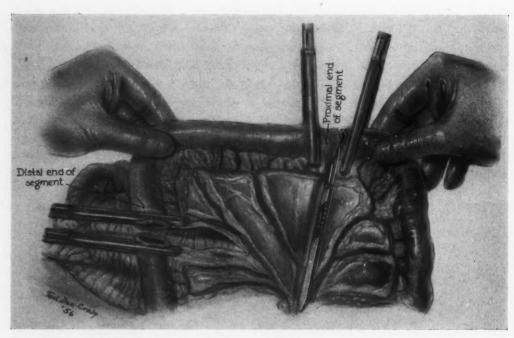


Fig. 2A.—Shows the technique of selecting the segment of ileum and division without crushing clamps.

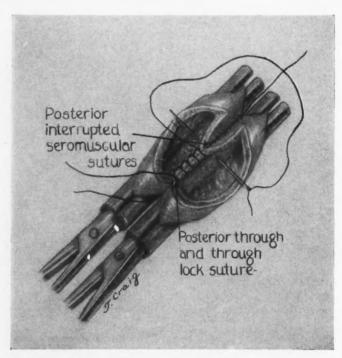


Fig. 2B.—Shows the technique of bowel anastomosis and closure used for the ileoileostomy, blind end of the proximal portion of the isolated ileal segment, and the ileosigmoid-ostomy. The ureteroileostomies were performed according to the technique of Cordonnier shown in Fig. 1.

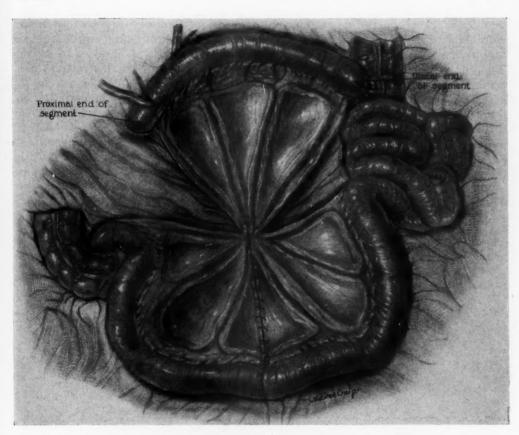


Fig. 2C.—Completed ureteroileosigmoidostomy in the dog. The ureters in the experimental animal from which this illustration was made are placed several centimeters from the line of closure in the proximal end of the ileal segment.

Experimental Ureteroileosigmoidostomy in Dogs

Theoretical Basis.—It has been postulated that a decrease in the numbers of sphincters and orifices which a patient or animal must attend to would be more desirable than an increase in their numbers; therefore, a return to ureterointestinal anastomosis of some sort. The theoretical basis for the procedure to be described centers about a "physiological valve" which could function so as to relieve back pressure upon the ureter, which results from contractions of the rectum and sigmoid, and as a filter for bacteria—a filter in that the flow of urine would be in a constant direction away from the ureters. A segment of terminal ileum has been selected to act as this physiological valve interposed between the urinary tract (the ureters) and the intestinal tract (the sigmoid colon). The terminal portion of the ileum has the slowest rate of rhythmic segmentation peristals of any portion of the bowel down to this point. It is also a less irritable portion of the intestine than the duodenum and jejunum, and possesses less resting tone. For practical purposes, peristalsis in the terminal portion of the ileum is unidirectional. When fluid or solid matter is placed in even the isolated segment of human or dog ileum, there results a peristaltic wave which follows the "law of the intestine," sisting of a ring of contraction which begins just above the point at which the bowel is distended and is immediately preceded by a ring of relaxation of the muscular wall of the small intestine. Thus, it has been conjectured that urine which would enter the upper (proximal) end of a closed segment of ileum would be propelled by an automatically produced double ring of contraction and relaxation, thereby carrying the fluid from the upper closed end of the proximal portion of the ileum into the sigmoid. Conversely, if intestinal contents should enter the distal portion of the ileum which is joined by an end-to-side anastomosis to the sigmoid colon, then there would be an immediate production of a double ring of contraction preceded by relaxation at the *lower* or distal end of the ileum which would result in expulsion by the ileum of the fecal material and its immediate re-entry into the large bowel. The unidirectional peristaltic characteristics of the terminal ileum and the response to stimuli in the form of a peristaltic wave are not dependent upon extrinsic innervation.



Fig. 3.—Completed ureteroileosigmoidostomy in the human. The ureters are joined to the uppermost portion of the isolated ileal segment by the technique of Cordonnier. The appendix, shown here, is removed. Placement of the ileal segment ventral and parallel to the sigmoid colon, and attachment of it loosely to the ventral wall of the sigmoid have been included to give stability to the ileal segment and to obliterate a potential blind pocket which might provide an opportunity for small bowel incarceration.

Peristalsis is inherent in the intestinal wall through the plexus of Auerbach.⁸ Therefore, ileal motility is assured even if the preserved extrinsic autonomic nerve connections are damaged during operation. It is probable that nitrogenous material and electrolytes such as the chloride ion are absorbed minimally from the terminal ileum, in comparison with the situation which is present in the duodenum, jejunum, and the upper ileum.⁹

Preoperative Preparation.—Mongrel dogs of 11 kilograms or more of body weight have been chosen at random for this operation. The operation has been

performed under sterile conditions following the induction of satisfactory general anesthesia consisting of intravenous or intraperitoneal pentobarbital sodium. A sterile bowel preparation has been attempted preoperatively with reliance mainly upon oral neomycin for suppression of the normal bacterial flora of the intestinal tract. The principal features of the preparation include the following:

- 1. Discontinuation of oral feeding 48 hours preoperatively, with the exception of oral neomycin.
 - 2. Administration of castor oil two times preceding the start of neomycin.
 - 3. Intravenous feeding during the 48 hours preceding operation.
- 4. Addition of Aureomycin and multivitamin substances with the intravenous feeding.

No preoperative pharmacological depressants have been utilized.

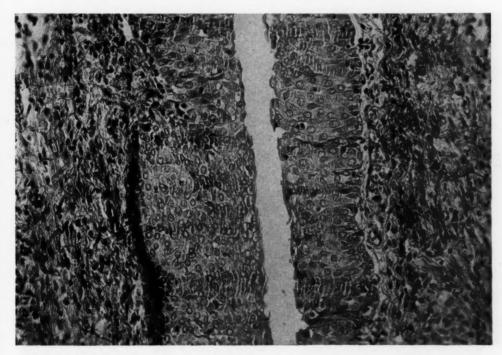


Fig. 4.—Photomicrograph of the dog ureter. The characteristic, normal-appearing lining epithelium of the ureter is seen in sagittal section in the center of this field. There are no prominent pathological changes. There is a minimal round-cell infiltration beneath the epithelial lining of the ureter on the left side. The remainder of the wall of the ureter is normal. Animal autopsied more than three months following ureteroileosigmoidostomy. (×400; reduced ¼.)

Technique.—A long midline lower abdominal incision is made through the ventral wall. Exploration of the peritoneal cavity is performed to exclude the possibility of gross intra-abdominal disease. The cecum is identified and the distal end of an ileal segment is selected at a point within 10 cm. of the cecum. The proximal end is similarly chosen. The ileum is divided at both points (Fig. 2A). The technique of end-to-end reanastomosis of the ileum is shown in Fig. 2B. With the proximal end of the isolated ileal segment closed by a double row of sutures, the distal end is joined to the sigmoid colon by an end-to-side technique similar to that used for the ileoileostomy. The operation is completed by bilateral end-to-side⁴ ureteroenterostomy (Fig. 2C). The ureters are joined to

the ileal segment near the proximal, closed end, within 1 cm. of the suture line (Fig. 3). A sterile rectal tube is left in place and the abdominal wound is closed in layers of interrupted sutures without drainage.

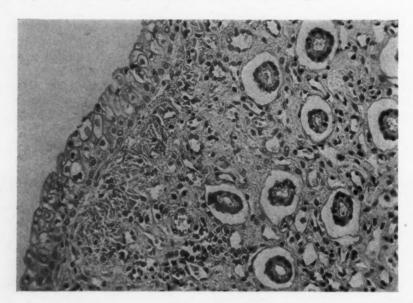


Fig. 5.—Photomicrograph of dog renal pelvis and medulla. The lining epithelium of the renal pelvis is preserved. There are no pathological changes of significance in the renal medulla. ($\times 200$; reduced $\frac{1}{4}$.)

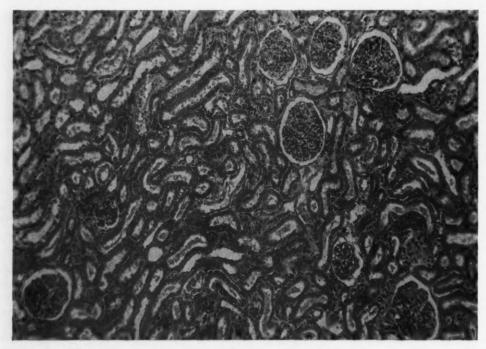


Fig. 6.—Photomicrograph of dog renal cortex. The glomeruli of the proximal tubules shown here have a minimal amount of round-cell infiltration and no other abnormal findings. This tissue, like that in Figs. 4 and 5, is from an animal autopsied more than three months following ureterolleosigmoidostomy. ($\times 400$; reduced $\frac{1}{4}$.)

Postoperative Care.—

1. No oral feedings 48 hours postoperatively.

2. Intravenous feedings during the first 48 postoperative hours with the addition of Aureomycin and multivitamin substances.

3. On the third postoperative day, clear fluids orally and oral suspension of antibiotic.

4. On the fourth postoperative day, soft diet with the addition of oral suspension of antibiotic.

5. Resumption of normal diet.

Oral intubation for decompression proximal to the ileoileostomy was not feasible in dogs. However, in no instance did any obstructive process occur.



Fig. 7.—The intravenous urogram on the left is that of the dog in which the technique shown in Fig. 2 was utilized. The pyelogram on the left side was made one month post-operatively and the one on the right six weeks later. The x-ray film on the right side shows an alteration in the right kidney and ureter which is typical of that which can be expected from the pressure of the ileal peristaltic wave. The hydroureteronephrosis and the connection between the right ureter and the segment of ileum at a point too far from the blind-end closure are shown here.

Comment

Successful ureteroileosigmoidostomy operations have been performed in dogs. Postoperative photomicrographs of the upper urinary tract of one of

the dogs are shown in Figs. 4, 5, and 6. In this animal a segment of ileum 25 cm. in length was used to join the ureters to the sigmoid colon. Such lengths are probably excessive and are thought to account for hyperchloremic acidosis. This opinion has been stated by Pyrah⁹ and is supported by our experimental observations not included in detail here. Another object lesson found in this particular animal is the gradual development of right-sided ureteral dilatation (Fig. 7). This condition will supervene whenever the ureter is anastomosed to the ileum several centimeters from the proximal, closed end of the intestinal segment.

Autopsy studies on all animals studied in this series of experiments have shown the ileal connecting segment to contain either clear urine or nothing. In no instance has fecal material been found in the ileum.

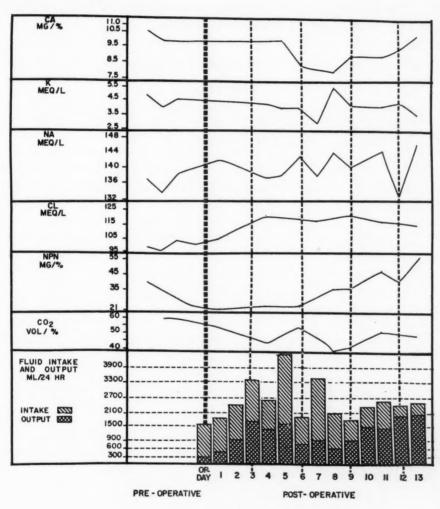
The results from ureteroileosigmoidostomies in dogs have led to a similar study in man. Three operations are summarized here:

CASE 1.—Patient A. R. (F.D.H. No. 2764) was a 64-year-old man previously treated by a variety of surgical operations for urinary incontinence and intractable stricture of the urethra. The ureteroileosigmoidostomy was performed as a single, elective surgical procedure. During the postoperative period the patient developed paralytic ileus which was controlled by conservative measures which included Miller-Abbott intubation. The urinary output as collected from the rectal tube was exceedingly good, and there was a noticeable lack of alteration in the electrolyte pattern of the blood (Fig. 8). This patient died of a pulmonary embolus two weeks after operation; this event permitted the rare observation of all of the anastomotic connections as well as the upper tract and bowel at autopsy performed two weeks following the operation. There were no unusual or abnormal findings in the kidneys, renal pelves, ureters, the ileal segment of bowel, or in any of the anastomotic connections.

CASE 2.—Patient A. M. (P.H. Unit No. 30-67-05) was a 46-year-old man previously treated for bladder tumor by two transurethral resections and two open surgical operations, the last of which was partial cystectomy. The ureteroileosigmoidostomy was performed at the conclusion of radical cystectomy for undifferentiated, recurrent carcinoma of the bladder. The electrolyte balance was almost identical with that in Case 1, which is shown in Fig. 8. The output of collected urine in the first 24 postoperative hours was 1,500 c.c., and exceeded 2,000 c.c. in every 24 hour period following that. The patient is alive and clinically well.

CASE 3.—Patient B. R. (F.D.H. No. 6433) was a 32-year-old woman who had been treated by a radical hysterectomy operation with bilateral pelvic lymph node resection 81/2 months prior to the development of a bilateral hydroureteronephrosis. This patient's original diagnosis was carcinoma of the cervix; secondary carcinoma was found in the left parametrium at the time of surgical pathological examination following radical hysterectomy. In addition, the ureterosacral ligament and right common iliac lymph nodes contained tumor. During the 8 months preceding ureteroileosigmoidostomy she developed, first, right hydronephrosis and, second, a nonfunctioning (by intravenous urography) left kidney. Ureteroileosigmoidostomy was performed, and the patient had no deviation from normal values for serum sodium, potassium, chloride, carbon dioxide, or nonprotein nitrogen. She made an uneventful recovery, and pyelography on the eighteenth postoperative day showed some return of function of the left kidney as demonstrated by the appearance of iodide in the 15 and 25 minute postinjection x-rays. This patient is of additional interest in that slightly more than one third of the lower ureter on each side was not thought suitable for use in the urinary diversion operation. Consequently a very high transection of each ureter was made before the severed proximal end was anastomosed to the closed end of the ileal segment.

Our purpose has been to determine from experimental surgery on dogs whether or not ureteroileosigmoidostomy is feasible for clinical trial in patients. No attempt has been made to solve all the specific problems associated with the operation in dogs.



TIME IN DAYS

Fig. 8.—Patient A. R., (F.D.H. Unit No. 2764). The immediate postoperative electrolyte and water balance is shown graphically here. In the bar charts at the bottom it is seen that there was an immediate output of urine which could be collected from the rectal tube. The postoperative urinary collection is far better than that which is commonly made from ureterosigmoidostomy patients.

The operation has been used in three patients, in connection with a large excisional operation for cancer and as the sole procedure. Its usefulness in urological, gynecological, and general surgery has not been determined. The principles upon which this experimental operation have been based are apparently sound. The results of a more extensive clinical trial will be reported in a subsequent communication.

Summary

- 1. A method of urinary diversion, ureteroileosigmoidostomy, is described.
- 2. The use of a segment of terminal ileum as a "physiological valve" between the ureter and sigmoid to relieve back pressure upon the ureter by utilizing the unidirectional peristaltic action inherent in this portion of the ileum is illustrated, both in humans and in dogs.
- 3. Evidence by photomicrographs, electrolyte studies, and autopsy findings of the feasibility of this operation is presented.

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THE RETAINED UTERINE CERVIX

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A^N unknown number of retained uterine cervices remain normal. Others bleed, lose support, or produce malignant growths. It is with this latter group that the present study is concerned.

From the year 1926 through 1951 the files of the Mayo Clinic contain the histories of 334 women who presented themselves for examination because of symptoms referable to such retained cervices which were subsequently removed or subjected to biopsy. Clinical histories were reviewed, as were the original microscopic slides. The surgical specimens were re-examined, and additional sections were made from four or more quadrants of the squamocolumnar junction of the cervix, the upper end of the cervical canal, and any grossly abnormal area. Biopsy material was recut if sufficient material was present. Paraffin embedding and hematoxylin and eosin staining were used. For presentation the cases have been separated into benign cervices and those containing a primary malignant growth. An interval of 2 years between the time of subtotal hysterectomy and appearance of the cervical malignant lesion was used as a measure of true primary malignancy of the retained cervix. This is the criterion set up by several who have reported this lesion.^{3, 5, 7, 9, 13, 24, 25}

The Benign Group

There were 256 patients whose cervices were histologically benign. Seventy per cent of the patients were in the 40 to 60-year age bracket, but more than 10 per cent were less than 30 years of age. Subtotal hysterectomy had been performed as early as 1914 or as late as 1947, with an average interval of 10 years between the two procedures.

The most frequent symptoms were vaginal bleeding, in 91 cases, and those related to prolapse of the cervix with attendant cystocele and rectocele, in 100 cases. "Vaginal discharge," "recent biopsy of the cervix reported as benign," pelvic pain, fear of a malignant lesion of the cervix subsequent to a malignant lesion of the removed uterine fundus, and vesicovaginal fistula were less frequent causes for seeking medical advice.

The cervical bleeding reported by the 91 patients began shortly after hysterectomy in some and appeared years later in others. Histologic examination of the cervical canal of those with bleeding disclosed the presence of endometrium in 40 instances (Fig. 1). The endometrium was atrophic in 25, proliferative in 11, and secretory in 4. The bleeding appeared irregularly in 46 patients, continuously in 10, on contact in 9, and with cyclic rhythm in 26. Those with cyclic

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bleeding all had some ovarian tissue present, and all but 5 had regular intervals of 24 to 30 days with scant-to-normal blood loss as compared with the preoperative menstrual flow. Where endometrial tissue lined the canal, it was equivalent to that found lining the uterine cavity and extended from varying levels in the cervical canal to distances of as short as 1 cm. to 2 mm. above the squamo-columnar junctional zone. This last measurement was made in 10 specimens. There was endometrial tissue in the cervical canal in 24 women who gave no history of bleeding.

Indications for surgical intervention were given as follows: bleeding in 71 patients, prolapse in 100, presence of a pelvic mass in 46, and inflammatory changes in 26. The presence of fistulas, endometriosis, a suspected malignant lesion, stenosis of the os, pelvic pain, and eradication of foci of infection each accounted for a small number of recommendations for surgery.

The abdominal approach was employed for the removal of the cervix in 72 cases because of the presence of a pelvic tumor or because of the need to repair fistulas (present in 3 patients). Unilateral oophorectomy in 53 patients and bilateral oophorectomy in 23 accompanied the removal of the cervix. Cystic oophoritis, hemorrhagic and follicular cysts were present in 56 specimens, endometriosis in 4, fibromas in 2, and a dermoid cyst in one. Malignant tumors involved the ovaries of 3 patients. One woman, who had solid ovarian grade 2 adenoacanthoma, was well 11 years later. The second patient, who had bilateral solid and cystic grade 3 cystadenocarcinoma and metastatic growths in the lymph nodes died of the tumor 1 year and 3 months after operation. The third woman, who had a papillary grade 1 cystadenocarcinoma of the remaining ovary, died in 5 years from recurrence of the tumor. The cervices in these 3 patients were benign.

Histologic examination of the cervix showed squamous-cell metaplasia in 27 instances, ulceration with necrotic surface and inflammatory changes in the base in 3 specimens, and endometriosis in 6 (Fig. 2). In one of these the endometriosis was superficial on the posterior surface of the cervix, but in the other 5 the endometriosis was deep in the wall of the cervix (Fig. 1). Inflammatory changes, mild to severe and primarily subepithelial, were present in 16 cervices. A clinical diagnosis of cervicitis and erosion of the cervix in 43 patients could not be confirmed histologically, but in other instances in which this diagnosis was made the microscopic findings were of papillary proliferation of the columnar epithelium at the squamocolumnar epithelial junction with growth of the columnar epithelium over the squamous epithelium and extending over the portio. Hyperplasia of the squamous epithelium was present in 19 cervices, and keratosis in 6.

Prolapse of the cervix, with accompanying cystocele and rectocele and the subsequent symptoms of discomfort, pain, and urinary dysfunction, was of sufficient degree to bring both the patient and the surgeon to the decision of surgical removal in 100 cases. Vaginal bleeding was a complicating factor in 35 of these. Prolapse of the uterus had been the surgical indication for subtotal hysterectomy in 28 of these patients. The subtotal procedure had been performed for the fibromyomas in 37 patients and for menorrhagia in 25. Fifty of these women were in the age group of 50 to 59 years at the time of the second operative procedure, 30 were 40 to 49 years of age, 18 were 60 to 69 years of age, and one each was 76 and 30 years of age. The mean interval between operations was 9.9 years, with a spread of 6 months to 34 years. All but 6 of the patients had borne children, one as many as 8, with an average family of 3. At the time of the removal of the cervix 41 of these women weighed more than 150 pounds, but the duration of this moderate to severe overweight was not known. Vaginal removal of the cervix with repair of the cystocele and rectocele was accomplished

in all of these 100 women. Mechanical failure returned in 9 women as early as 2 years or as late as 15 years after the operation. An enterocele developed in 5 women, complete prolapse of the vagina in 2, cystocele in one, and urinary incontinence in one.

Follow-up studies on the patients whose retained cervices showed no malignant tissue revealed that 5 had subsequently succumbed. In 2 the cause of

Fig. 1.

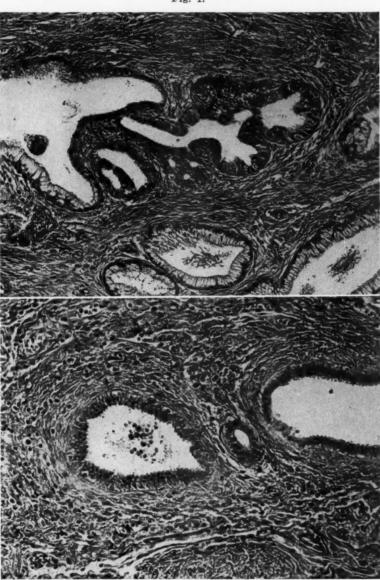


Fig. 2.

Fig. 1.—An endocervical gland contains both endometrial type of epithelium and usual columnar mucous epithelium, suggesting a possible origin of endometrial elements found in the cervical wall in 5 patients. (Hematoxylin and eosin; ×135.)

Fig. 2.—Area of endometriosis deep in the wall of a retained cervix. Epithelium is endometrial in type, but stroma is somewhat more compact than normal. (Hematoxylin and eosin; ×150.)

death was extension of ovarian cystadenocarcinoma, as previously described. In the third case, melanoma of the right great toe produced generalized metastasis and death 2 years after the cervix was removed. The fourth woman died of lymphoblastoma 8 years after operation. The cause of death of the remaining patient was not ascertained. No operative deaths occurred in these 256 patients.

The Malignant Group

Carcinoma was present in the retained cervices of 78 of the entire group of 334 women. Sixty-two of these were squamous epitheliomas, 13 were adenocarcinomas, one was an adenoacanthoma, and 2 cervices contained multiple tumors. The adenoacanthoma exhibited the characteristic admixture of adenocarcinoma and squamous-cell carcinoma. We graded it 2 by the Broders method. Of the 2 cervices which contained multiple tumors, one contained both cell types, adenocarcinoma, grade 2, and squamous-cell epithelioma, grade 3, but the failure of complete mixing suggested independent origins. The other cervix had two distinct tumors, an adenocarcinoma, grade 1, of the upper end of the cervical canal and a squamous-cell epithelioma, grade 3, of the lower portion. For statistical purposes the 2 cases of multiple tumors have been classified according to the dominant cell type, which was squamous epithelioma, grade 3.

When the cervical carcinoma was diagnosed (Table I), the peak incidence was in the 50 to 59 year age group. On an average the subtotal hysterectomy had been performed 10 years previously, none less than 2 years. All but one of the patients were married. There were 24 (31 per cent) nulliparas, 8 primiparas, and 46 multiparas.

TABLE I. AGE OF PATIENTS AT OPERATION AND SUBSEQUENT DIAGNOSIS OF CARCINOMA

AGE (YEARS)	AT TIME OF SUBTOTAL HYSTERECTOMY	AT TIME OF DIAGNOSIS OF CARCINOMA OF CERVIX
 10-19	1	
20-29	5	
30-39	26	2
40-49	33	25
50-59	11	32
60-69	2	18
70-79		1

TABLE II. INDICATIONS FOR SUBTOTAL HYSTERECTOMY IN THOSE WHO DEVELOPED CARCINOMA
OF THE RETAINED CERVIX

INDICATION	PATIENTS
Fibromyoma	28
Fibromyoma with menorrhagia	11
Menorrhagia	6
Postmenopausal bleeding	2
Malignant lesion of uterus	1
Malignant lesion of ovary	1
Postirradiated carcinoma of cervix	1
Pelvic inflammatory disease	3
Cystic ovary	1
Pelvic pain	1
Hypertension	1
Acute appendicitis	1
Prolapse of uterus	1
Unknown	20

Fibromyoma, either with or without menorrhagia, was the most frequent indication for the initial procedure of subtotal hysterectomy (Table II). Five of the 78 removed fundi contained an adenocarcinoma. One of these has been

described earlier in this paper as having developed an adenoacanthoma in the retained cervix and 2 others multiple tumors of squamous and columnar epithelial cells. The intervals between operative procedures in these three

Fig. 3.

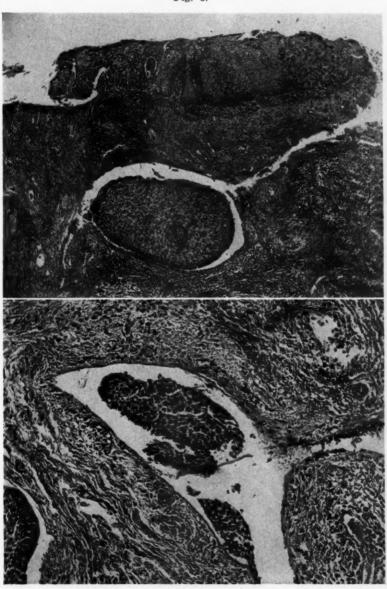


Fig. 4.

Fig. 3.—Invasive grade 3 squamous-cell epithelioma of the cervix associated with in situ carcinoma of the overlying epithelium. Note the lymphatic channel plugged with carcinoma. (Hematoxylin and eosin; ×50.)

Fig. 4.—Grade 3 squamous-cell epithelioma in a retained cervix. (Hematoxylin and eosin; ×150.)

were 16, 10, and 2 years. The remaining 2 cervices in this group of 5 cancerous fundi produced squamous-cell carcinoma. Of these 5, the patient with the adenoacanthoma died in 9 months from metastasis to the abdomen, lungs, and

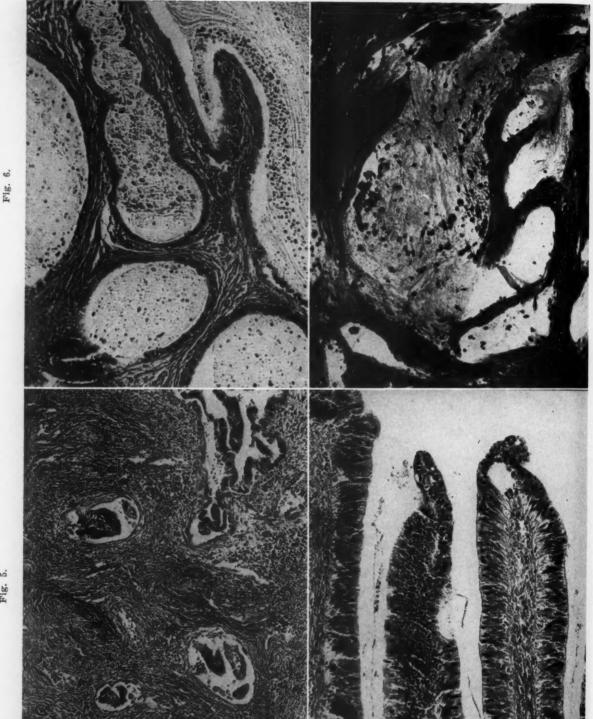


Fig. 5.

supraclavicular lymph nodes, the metastasis being adenocarcinoma; another who had one of the double tumors and a third patient who had squamous-cell epithelioma died in 3 years; the other patient with two separate tumors in the cervix was still living at 3 years and 7 months; the fifth patient could not be traced.

Vaginal bleeding was the presenting symptom in 61 of the 78 women with carcinoma of the cervix. The bleeding was sometimes continuous but on other occasions it was intermittent and irregular; it was usually scanty but occasionally profuse. Some patients had had bleeding for at least 5 years, others only for 4 days, the average duration being 11.9 months, and many had the symptom for less than 6 months. Eight women asked for an evaluation of previous treatment of carcinoma of the cervix; 12 had had a diagnosis of carcinoma by biopsy before presenting themselves for examination; 3 had had a clinical diagnosis of carcinoma of the cervix. In addition to a diagnosis of carcinoma by biopsy 5 patients had received irradiation therapy. The treatment had been within a year before admission, except for one patient, who had received such treatment 20 years previously.

Physical examination showed almost uniformly a firm cervix with or without ulceration and with tumefaction involving only the cervix, extending to the vaginal fornices, progressing to the broad ligaments or fixing the entire pelvis. Two lesions which proved to be in situ growths were described on examination as bleeding on manipulation and 3 others as "cervicitis," "lacerated cervix," and a "polypoid growth." The growths were classified by the criteria of physical findings as set down by the League of Nations for staging the extent of a tumor, and a biopsy was taken either in the office or in the operating room. In 69 cases, biopsy only was performed. In 5 the cervix was removed vaginally and in the remaining 4 the cervix was removed abdominally. Additional operative procedures included colostomy to relieve a stricture in one case and a radical Wertheim dissection in another.

Microscopically, the in situ lesions had the cellular picture of cervical malignancy, with increase in cell size, enlarged hyperchromatic nuclei, alterations of polarity of cells, and the presence of mitotic figures; all changes were limited to the squamous superficial layers. The infiltrative squamous-cell carcinomas exhibited the same changes but with extension to various depths in the wall of the cervix and even beyond the limits of the cervix (Figs. 3 and 4). The adenocarcinomas were for the most part papillary, and there was marked production of mucus in one tumor (Figs. 5, 6, 7, and 8). The columnar cells had enlarged, hyperchromatic nuclei with migration of these nuclei from the cell base; layering of the columnar cells was observed routinely. Both tumor types were graded as to degree of malignancy according to the classification of Broders. In situ malignant changes were seen in the margins of infiltrative tumors in 10 of the squamous-cell epitheliomas. Clumps of malignant cells in lymphatic vessels were frequent in both squamous-cell and columnar-cell carcinomas which were not in situ.

The postoperative management included combined radium and roentgen therapy for 65 of the patients, radium therapy alone for 5 patients and deep

Fig. 5.—Grade 2 adenocarcinoma involving the lymphatics adjacent to its primary site in a retained cervix. (Hematoxylin and eosin; $\times 100$.)

Fig. 6.—Grade 1 mucus-producing adenocarcinoma primary in retained cervix. (Hematoxylin and eosin; $\times 200$.)

Fig. 7.—Same lesion as in Fig. 6, demonstrating papillary features and cellular detail. (Hematoxylin and eosin; $\times 150$.)

Fig. 8.—Grade 2 adenocarcinoma primary in retained cervix, which produced excessive amounts of mucus with relatively scant numbers of malignant epithelial cells. (Hematoxylin and eosin; $\times 150$.)

TABLE III. DEATH OR SURVIVAL OF 78 PATIENTS WITH CARCINOMA OF THE RETAINED CERVIX ACCORDING TO THE STAGE OF THE MALIGNANT TUMOR

	NUMBER	DIED		SURVIVING		
STAGE		LESS THAN 5 YEARS	MORE THAN 5 YEARS	LESS THAN 5 YEARS	MORE THAN 5 YEARS	NOT TRACED
I	10	1		2	7	
II	24	3	2	6	12	1
III	25	9	3	2	11	
IV	12	8	1		1	2
0	5			1	4	
9	2	1			1	
Total	78	22	6	11	36	3
		6	28	4	17	

Table IV. Death or Survival of 78 Patients With Carcinoma of the Retained Cervix According to the Type and Grade of the Malignant Tumor

		D	IED	SURV	IVING	
TYPE AND GRADE*	NUMBER	LESS THAN 5 YEARS	MORE THAN 5 YEARS	LESS THAN 5 YEARS	MORE THAN 5 YEARS	NOT TRACES
SCE 2	4	1	2		1	
SCE 3	47	12	3	8	24	
SCE 4	13	3		3	4	3
Adca 1	7	3			4	
Adca 2†	5	2	1		2	
Adca 3	1				1	
Adca 4	1	1				
Total	78	22	6	11	36	3
		- 2	28	4	17	

^{*}SCE = squamous-cell epithelioma; Adca = adenocarcinoma.

Table V. Death or Survival of 78 Patients With Carcinoma of the Retained Cervix According to Stage, Type, and Grade of the Malignant Tumor

	STAGE	TYPE AND GRADE*	TOTAL	DEAD	ALIVE	NOT TRACED
I.	Total 10†	SCE 3	6		6	
		Adca 1	3		3	
		Adca 2	1	1		
II.	Total 24‡	SCE 2	2	1	1	
		SCE 3	12	2	10	
		SCE 4	6		5	1
		Adca 1	2	1	1	
		Adca 2	2	1	1	
III.	Total 25§	SCE 2	1	1		
		SCE 3	16	7	9	
		SCE 4	4	2	$\begin{smallmatrix}9\\2\\1\end{smallmatrix}$	
		Adca 2	$\frac{4}{2}$	1		
		Adca 3	1		1	
		Adca 4	1	1		
IV.	Total 12	SCE 2	1	1		
		SCE 3	7	6	1	
		SCE 4	3	6		2
		Adca 1	1	1		
0.	Total 5	SCE 3	5		5	
1.	Total 2	SCE 3	1		1	
		Adca 1	1	1		

^{*}SCE = squamous-cell epithelioma; Adca = adenocarcinoma.

[†]One adenoacanthoma included.

[†]Includes one case with both SCE 3 and Adca 1.

[‡]Includes one case with both SCE 3 and Adca 2.

[§]Includes one case with adenoacanthoma 2.

roentgen therapy alone for one patient. Five patients received no irradiation therapy; these included 2 who had in situ lesions, one who underwent a radical lymph node removal, one with a grade 1 adenocarcinoma, and one who had a stricture of the intestine. Two patients received treatment elsewhere.

The carcinoma of the retained cervix was fatal in 28 (36 per cent) of the 78 women studied; 22 of these women died in less than 5 years after treatment had been given. Three women were alive but with recurrences of the tumor present in this same 5 year period. Thirty-six (46 per cent) were alive 5 years or more after they received treatment; 11 patients were alive less than 5 years after treatment. Three patients could not be traced. The highest death rate was in the stage II and III lesions, which proved fatal in 17 of 49 cases so diagnosed. Although only 14 patients had adenocarcinomas and 12 of these were graded 1 or 2, nevertheless, 50 per cent of these patients succumbed. The one patient with adenoacanthoma died in 9 months from widespread metastasis. The larger group (62 patients) with squamous-cell carcinoma and 2 patients with coexisting squamous-cell carcinoma and adenocarcinoma had a death rate of 33 per cent. Forty-seven of these 62 squamous lesions were graded 3. Tables III, IV, and V depict these results.

Comment

For more than 30 years gynecologic surgeons have advised that total rather than subtotal removal of the uterus be performed if hysterectomy is the indicated operation.^{1, 2, 6} For the patients in whom it is not possible to remove the cervix it has been recommended that thorough curettage of the cervical canal and conization of the external os be additionally performed to denude these zones of all epithelium. But Masson¹⁷ pointed out that this does not eliminate the danger of the subsequent development of carcinoma from the squamous epithelium of the portio that remains. As early as 1927 he reported a mortality rate of 1.3 per cent for total hysterectomy performed in 229 instances during that year and 1.8 per cent for subtotal hysterectomy done in 217 cases over the same period. The present-day status of blood banking, chemotherapy, and antibiotic therapy has helped to bring this mortality rate to well below 1 per cent for almost all gynecologic surgeons. All agree that skilled surgeons should be performing the operation.

The present study of benign retained cervices emphasizes that the cervix which has lost its support or which bleeds is the one which leads to most discomfort, disability, and anxiety.^{22, 23} Surgical removal of such cervices made them available for a complete search for the presence of a malignant lesion and at the same time offered opportunity to carry out an oftentimes needed vaginal repair. The microscopic study of the cervical canal, which demonstrated endometrial tissue extending down the canal to within 2 mm. of the squamocolumnar junction in 10 cases, diminishes the expectancy of removing sources of bleeding by removal of the uterine fundus only. This endometrial tissue was probably the source of endometrial glands and stroma, which were found in 5 instances deep in the wall of the cervix in much the same manner as when internal endometriosis or adenomyosis is found in the wall of the uterine fundus. Endometrial tissue on the posterior or peritoneal surface of the cervix, on the other hand, suggested that it was of ectopic origin and part of a pelvic endometriosis.

Prolapse of the cervix over a prolonged period, with the attendant increased trauma to the vaginal portio, apparently did not increase the incidence of carcinoma in the cervix, for 100 of the patients in this series had various degrees of loss of support with no associated malignant changes. The patients who did have carcinoma of the cervix did not exhibit prolapse and were found on examination to have very minor degrees of loss of support.

Vaginal removal of the cervix gave the best access for repair of the supports of the vagina, but when a pelvic mass or a fistula into the cervix required an abdominal approach a satisfactory repair of vaginal support could be made from above. Mechanical failure occurred in only 9 of the women who were treated by removal of a benign cervix. All had a preoperative complaint of cervical prolapse.

The reported frequencies with which carcinoma begins in the retained cervix have been based on the number that occur compared with all carcinomas of the cervix diagnosed during an identical period of time at the same diagnostic center. In 1953 Young and Jonas²⁷ compiled these reports and found an average incidence of 4.1 per cent. Meigs²⁰ based his figure of 0.73 per cent on the number of lesions that developed after subtotal hysterectomy as observed in his own series of cases. From our own standpoint we were unable to make any satisfactory statistical analysis regarding incidence of cervical carcinoma complicating operation which involved preservation of a cervical stump. We do consider it significant and very important that no less than 23 per cent of cervical "stumps" which produced symptoms that brought the patients to the clinic for treatment were in fact the seat of primary malignant disease.

Some authors^{10, 14, 20, 26} have accepted an arbitrary interval of 1 year from the time of a subtotal hysterectomy to the time of diagnosis of carcinoma of the cervix as the criterion for judging a carcinoma to be primary in the retained cervix and not present at the time of hysterectomy. Others^{4, 15, 16} prefer a 3 year interval, while Hendricks¹² used a 5 year time lapse. The majority of authors^{3, 5, 7, 9, 13, 24, 25} use a 2 year base line. The present series includes those cervical carcinomas that were diagnosed 2 years or more after the subtotal hysterectomy had been performed. This interval was used with the knowledge that there is a growing literature on cervical carcinomas known to have been in situ for much longer periods before clinical symptoms and lesions occurred.

The average interval between operative procedures was 10 years for both benign and malignant lesions, with an average age at diagnosis of cervical carcinoma advanced approximately a decade from the age at diagnosis of those in the intact uterus. The nulliparity (31 per cent) of this group of women, all but one of whom were married, is higher than the 22 and 9 per cent given by others. Maliphant based his 37 per cent of squamous-cell epitheliomas and 50 per cent of adenocarcinomas on infertility rather than absolute nulliparity.

The 5 year survival rate of 46 per cent is better than the average of 35 per cent given for all carcinomas of the cervix.8, 11, 18, 19, 21 Both radium and deep roentgen therapy were given to 65 patients. Vaginal excision of the cervix was performed for 3 of 5 patients with in situ carcinomas. The tumor in these 3 was grade 3 squamous-cell carcinoma; combined radium and roentgen therapy was given additionally to one of these patients. Three are living and well at 4.7 years, 6 years, and 12 years later, respectively. The other 2 patients had in situ carcinoma and received radium and roentgen therapy for grade 3 squamous-cell epitheliomas; they were well after 7 and 10 years, respectively. These patients with in situ carcinoma were studied in the era prior to the institution of our current program of cytodetection, and the line of treatment employed does not reflect our present policy. Two early stage I carcinomas were treated by vaginal excision. One patient with a grade 3 squamous-cell epithelioma received radium therapy postoperatively and was well 5 years later. The other patient had both a grade 3 squamous-cell epithelioma in the portio of the cervix and a grade 1 adenocarcinoma of the upper portion of the cervical canal. This patient received both radium and roentgen therapy and was well 3 years and 7 months after operation. Abdominal excision was performed for 4 patients. One of the 4, with a stage I, grade 2 adenocarcinoma, received radium and roentgen therapy after abdominal excision of the cervix and lived only 1 year and 8 months. A radical Wertheim operative procedure was considered the best choice of treatment for the second patient, who had a stage I, grade 3 squamous-cell epithelioma. No radiation therapy was given, and she could not be traced after 1 year. The third patient had an unstaged grade 1 adenocarcinoma of the cervix and an abdominal fistula. A loop colostomy was necessary to relieve obstruction due to a stricture; she was given no subsequent therapy and died in 3 years. There was a stage I, grade 1 adenocarcinoma in the cervix of the fourth patient who underwent abdominal excision of the cervix. She was well after 5 years, having received no further treatment.

The mortality was highest in the stage III and IV lesions of squamous-cell epithelioma, grade 3, a total of 13 patients. However, such advanced carcinomas, in a few patients, did respond to irradiation therapy. For example, a 56-year-old woman had undergone subtotal hysterectomy for fibromyoma 17 years before she was admitted with a history of 3 months of vaginal bleeding. Three years previously there had been vaginal bleeding, for which she had received roentgen therapy. The lesion was staged as IV and, on biopsy, was diagnosed as squamous-cell carcinoma, grade 3. The patient received combined radium and roentgen therapy; 10 years later the result of her examination was "negative." Another woman, 67 years of age, who had undergone subtotal hysterectomy for fibromyoma 14 years previously, had experienced vaginal bleeding for 18 months. The lesion was staged as III with a diagnosis, based on biopsy, of grade 3 squamous-cell carcinoma. She received combined irradiation therapy and 10 years later was in good health. Twenty-four years after subtotal

hysterectomy a 54-year-old woman was admitted complaining of vaginal bleeding for 3 months. She was found to have a stage IV, grade 3 squamous-cell epithelioma which had invaded the bladder with obstruction to the right ureter and hydronephrosis. She also received radium and roentgen therapy. An examination 8 years later showed a normal pelvis and urinary tract, but there was a question of the presence of a brain tumor. She died 2 years later without a further diagnosis. Another 54-year-old woman, who exhibited a stage III, grade 3 squamous-cell carcinoma, gave no response to repeated therapies with combined irradiation. Eight years before, she had undergone subtotal hysterectomy for fibromyoma, at which time the cervix was coned and no malignant lesion found. Over a period of 3 years she received therapy with repeated examinations and biopsies showing no abatement of the carcinoma until she died of it at the end of that time.

Adenocarcinoma was diagnosed in 14 cases, 18 per cent of the 78 carcinomatous cervices. Seven of these were grade 1, 5* were grade 2, one was grade 3 and one grade 4. In this small group the mortality was high; half of the patients died and all but one before the first 5 year posttreatment stage—4, 7, and 9 months, 1, 2, 3, and 11 years after treatment. Combined irradiation therapy had been given to 5 and one had received radium therapy. The seventh patient died of a pulmonary embolus while receiving therapy for a metastasis to the ilium. The staging and treatment were comparable in those who lived and those who died, with a slight margin of two more tumors in stage I in those who survived.

By statistical reckoning the 28 women who died from carcinoma of the retained uterine cervix comprised but a very small portion of all the women who have carcinoma of the cervix. However, their deaths could have been prevented by adequate surgical treatment which could have been performed at no added risk. Moreover, the saving of months and years of discomfort and anxiety for the women whose benign retained cervices gave symptoms could have been made possible by a complete initial operation.

Summary

- 1. The case histories of 334 patients for whom the retained uterine cervix had been surgically removed or subjected to biopsy were reviewed and the surgical material was studied.
- 2. These cases represent the women who had a sign or symptom referable to the retained cervix which caused them to ask for examination.
- 3. Of this group 78 women (23 per cent) had a carcinoma of the cervix and 36 per cent of these carcinomas caused the death of the patient.
- 4. Carcinomas of stages III and IV and squamous-cell epitheliomas, grade 3, were responsible, percentage-wise, for the largest number of deaths.
- 5. Adenocarcinoma, even of grade 1, caused a proportionally high mortality—death in half (7) of the 14 patients so afflicted.

^{*}One grade 2 adenoacanthoma included in this group for statistical reasons.

- 6. Adenoacanthoma was the tumor type encountered in one cervix, and 2 cervices contained both a squamous-cell carcinoma and an adenocarcinoma.
- 7. Prolapse of the cervix and vaginal walls constituted the complaints and findings present in 100 patients.
- 8. Cervical bleeding was the most frequent presenting symptom in both benign and malignant cervices.
- 9. Endometrium was found lining the cervical canal in 64 specimens, and there had been some type of bleeding associated with 40 of these. This endometrial tissue was found to extend as far distal as 1 cm. to 2 mm. above the squamocolumnar junction.
- 10. Although abdominal removal of the cervix was done when pelvic masses and fistulas were present, the vaginal approach was considered to be of advantage in that more adequate repair of the vaginal wall could be done. This was of particular advantage in the 100 cases of prolapse of the cervix with accompanying cystocele and rectocele.
- 11. Except in rare cases of very difficult procedures, the results of the present study indicate that, when hysterectomy is the choice of treatment, a total removal of the uterus is advisable.

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A DISCUSSION OF THE MANCHESTER OPERATION*

Report of 380 Cases

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In THE United States, interest in the Manchester operation has grown greatly since reports of its performance appeared in our literature about two decades ago. The operative treatment of prolapse of the uterus had been, for the most part, colporrhaphy with shortening of the round or uterosacral ligaments, frequently suspension or fixation of the uterus, or even bisection of the corpus with wide anchorage to the abdominal aponeuroses. Vaginal hysterectomy, interposition, and colpocleisis were favored for special indications. The Manchester operation had not found favor here though it had been performed in Great Britain for nearly fifty years.

In 1932, however, Maier and Thudium³ and Frank⁴ reported great satisfaction with this operation; and in 1935 Gordon⁵ reviewed the results of 152 Manchester operations, the earliest performed in 1917. Again, in 1946, Gordon⁶ reported a series of 206 Manchester operations with special reference to parturition and total prolapse.

Material

This report covers the experience of a third decade, 1944 to 1953, in which 453 operations for prolapse of the uterus were performed in the Department of Obstetries and Gynecology of St. Catherine's Hospital. In 380 cases the operation was a typical Manchester. In the others, vaginal hysterectomy or other procedures were carried out. In a few an interposition was combined with the Manchester operation. No round ligament or uterine suspension operation was performed (Table I).

TABLE I. TOTAL OPERATIONS FOR PROLAPSE OF UTERUS, 1944-1953

Manchester	380
Vaginal hysterectomy	36
Interposition	16
Le Fort	3
Spalding Richardson	2
Manchester and subtotal hysterectomy*	16
 Total	453

^{*}Leaving isthmus.

Presented at a meeting of the Brooklyn Gynecological Society, Oct. 17, 1956.

The 380 cases in which typical Manchester operations were performed are the basis for this report. No patient in whom the cervix had not descended well down the vagina is included. Seven of the women were nulliparous. A previous operation for uterine prolapse had been performed in 38 cases. Prolapse of the vaginal vault had followed supravaginal hysterectomy in 26 cases and total hysterectomy in 8 cases.

Since the risk of operation was not thought to be great, no patient was rejected. Ten women had diabetes. Obesity was often associated with prolapse, and hypertensive disease commonly. The ages of all these women, as well as of those in special subgroups, are shown in Table II.

TABLE II. AGE OF 380 PATIENTS TREATED BY THE MANCHESTER OPERATION

AGE IN YEARS	TOTAL NUMBER	WITHOUT AMPUTATION OF CERVIX	PROCIDENTIA	EXTROVERSION OF VAGINA
20-30	4	2		
31-40	51	5	2	
41-50	102	11	6	4
51-60	128	16	16	2
61-70	77	5	11	4
71-80	15		8	
Over	3		2*	
Total	380	39	45	10

*Ages 85 and 86.

The great majority of operations were performed under local Novocain infiltration, preceded by heavy basal morphine and seopolamine.

Mortality and Morbidity

There was one death after a Manchester operation. In 1947 a patient 74 years of age died of acute renal failure nearly three weeks after operation.

Postoperative complications were comparatively few, except that low-grade vaginitis with foul discharge, perhaps slight fever, was fairly common. Parametritis was reported 4 times, and in 2 cases a subvaginal abscess broke through the suture line. Pelvic peritonitis followed one operation, and thrombophlebitis with pulmonary infarct another. Pyometra complicated one case. In 2 cases severe late hemorrhage, one with shock, was due to infection. In 4 cases vaginal bleeding due to poor hemostasis occurred within a few hours of operation.

End Results

Study of the immediate results of a large number of Manchester operations performed by operators of varying degrees of ability and experience proves the comparative safety of the procedure. Statistics of cure, to be of value, must take into account wide variations in the anatomical conditions encountered by the operator, his experience with vaginal plastic surgery, his interest in various ways of curing prolapse, and perhaps his attitude toward preservation of the reproductive faculty. Then, too, a variable number of years must pass before success of an operation for prolapse is assured. Comparison of end results of different clinics, different operators in the same group, and the time factor itself make the value of all statistics somewhat doubtful.

In 108 cases, follow-up has been sufficiently close and personal to warrant report on the end results of the Manchester operation. All of these were private patients operated upon by us and observed by us at intervals for at least 2 years, many for 5 or 6 years, and some for as long as 12 years. The nature of our clinical material in this series of 108 patients is shown in Table III.

TABLE III. CLINICAL DETAILS OF 108 PATIENTS WITH PERSONAL FOLLOW-UP OBSERVATIONS

AGE IN YEARS	NUMBER OF OPERATIONS	WITHOUT AMPUTATION OF CERVIX	CERVIX AT INTROITUS	PROTRUSION OF CERVIX	PROCIDENTIA	EXTROVER SION OF VAGINA
30-40	13	2	9	7		
41-50	24	5	11	6	2	3
51-60	37	15	6	8	6	
61-70	29	2	3	5	7	5
71-80	4				2	1
Over	1				1*	
Total	108†	24	29	26	18	9

*Age 85.

†Six patients had diabetes.

Prolapse of the uterus was cured, in that the uterus remained at a good level, in every case. In cases with procidentia and extroversion the results were also uniformly satisfactory. Certain faults and later complications may be listed as follows:

- 1. Dyspareunia due to annular vaginal cicatrix just below the uterus (1 case).
 - 2. Short vagina, no complaint from patient (3 cases).
- 3. Stenosis of os in cervical stump required occasional dilatation for dysmenorrhea until menopause (1 case).
- 4. Cystocele, 4 cases; one appeared 3 years after operation, and one 10 years afterward; 2 were immediate failures.
- 5. Stress incontinence, 6 cases; one appeared 6 years after operation; 5 were operative failures.
- 6. Enterocele, 4 cases; one appeared 2 years after operation, and another 10 years afterward; two were operative failures.
- 7. Abdominal hysterectomy had to be performed in one patient at the age of 39 years, 7 years after the Manchester operation. Normal delivery at term had occurred in the meantime.
- 8. A Manchester operation with partial amputation of the cervix at age 33 years was followed one year later by delivery of a fetus that weighed 5,200 grams, and a spontaneous abortion a few years later. The result of the Manchester operation is still good 9 years after operation.

Persistence of cystocele after the Manchester operation is due to poor closure of the vaginal defect, or to infection and breakdown of the repair. Stress incontinence is a difficult problem at best, and particular attention must be paid to it. Enterocele is said to develop rarely after the Manchester, but our experience is that enterocele is not always easy to recognize, and failure to tie off a small hernial sac will inevitably lead to its pouching downward and eventual protrusion. We now open the cul-de-sac to be sure of its recognition.

Our operative procedure otherwise closely follows that of Fothergill whose diamond-shaped denudation prepares the vagina for easy closure. Suture material is light chromic catgut, and we do not bury sutures. We

have found local anesthesia very satisfactory. Only occasionally is postoperative catheterization a problem, so an indwelling catheter is not used at operation. Once these patients were kept in bed for 10 to 14 days, now they are walking about in a day or two.

Procidentia

In procidentia, that awe-inspiring term for total prolapse, the entire uterus must be found outside the vulva. The surgical problem is no different, however. Excellent results followed the Manchester operation in 18 women with procidentia, 6 of whom had diabetes. Slightly more than half of these patients were more than 60 years of age. In 3 of these cases, however, prolapse of the uterus was not total, but nearly so. Berwind⁸ calls this subtotal prolapse. He reports satisfaction with the Manchester operation in 93 such cases, and 26 cases of total prolapse.

Extroversion of the Vagina

Although variously called inversion⁹ and eversion¹⁰ of the vagina, extroversion appears to be a better term. It is significant that it occurs most often when hysterectomy has been supravaginal. It is truly total prolapse, though it does not conform to the classic definition of procidentia. Enterocele often associated with it may contain sigmoid colon and small bowel as well.

The Manchester procedure will give satisfactory results in these cases, since the lateral vaginal fornices are supported by the transverse cervical ligaments. If the cervix is present the transverse cervical ligaments may usually be found. If not, shortening of the parametrium of the lateral fornices with subsequent scarring may be relied upon to lift the vaginal vault.

In 9 cases of extroversion of the vagina, in 6 of which the cervix was absent, results were satisfactory.

The Manchester Operation in Young Women

Objection to the Manchester operation is, we believe, principally related to amputation of the cervix, yet excellent results may be had without amputation of the cervix. The operation is nonetheless a Manchester. Fothergill, how himself often did not remove the cervix, stated, "When the wound is closed from side to side, the tissues which lay at the side of the cervix are united in the middle line in front of the cervix which is then pushed backwards into the hollow of the sacrum." No more interesting portrait of genital prolapse and the nature of its relief by operation has ever been made than Fothergill's. Those who will take the trouble to resurrect this material will find it a rewarding experience.

As a matter of fact, amputation of the cervix, when performed, is nearly always incomplete, a centimeter or two below the level of the internal os. Decision to remove the cervix, or how much of it to remove, depends upon its length and the condition of the portio. If lengthening is due to hypertrophy, usually supravaginal, access to the transverse cervical ligaments cannot be had without amputation. Often the cervix of the postmenopausal woman is small, however, and amputation not only adds a little to the risk of operation but is actually unnecessary.

Muscle which originates in the uterus is consistently found in the base of the broad ligaments and in the uterosaeral ligaments. Smooth muscle lies also between the pelvic portion and the superior surfaces of the levator ani as a series of bundles which radiate from the uterus at the level of the internal os.¹³ The Mackenrodt and uterosaeral ligaments are extremely strong

bands which blend fanwise and are attached to the uterus through its outer coat at the level of the internal os. The terminal fibers of the uterosacrals have been shown to decussate freely with each other on the back of the uterus, fanning out greatly and bridging over the lower and upper uterine segments in the third month of pregnancy. This arrangement is presumably duplicated in the transverse cervical ligaments.14 This is a fact of prime importance in the management of prolapse during the reproductive period of life.

In young women total prolapse of the uterus is rare, yet it does occur. and in these cases amputation of the cervix should not be performed without full consideration of its implications. The hazards of subsequent pregnancy are slight if the cervix has not been amputated. Many pregnancies after Manchester operations have been reported. 6, 15, 16

Vaginal plastic repair combined with some type of intra-abdominal operation offers no more than a Manchester. Shortening the round ligaments, it is true, will correct retroversion but, if the uterus can be maintained at its proper level, retroversion is of no importance in these young women.

Hunter, 17 once an assistant of both Donald and Fothergill, still prefers to call the operation Fothergill, not Manchester. He is of the opinion that all vaginal operations in young women are in the nature of compromise, and whatever we do there is some risk of recurrence if pregnancy supervenes. That slight risk might well be taken, we believe, since the alternatives to the Manchester operation are living with a pessary or undergoing vaginal hysterectomy.

Conclusion

This study adds 380 Manchester operations to 358 previously reported. Excellent results have been had in the treatment of prolapse of the uterus, particularly procidentia and extroversion of the vagina.

Inevitably gynecologists will differ as to the operation they prefer for uterine prolapse. After close examination of the end results the advantages of the Manchester operation are very apparent to us.

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32 REMSEN STREET

CONGENITAL ABSENCE OF THE VAGINA

An Analysis of Thirty-Two Cases Corrected by the McIndoe Operation

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THE unfortunate embryological omission of a vagina has stimulated the inventive genius of gynecological surgeons for the past half century. The methods recommended for the formation of an artificial vagina have become simpler and safer and have yielded better results, but even today there is still no unanimity of opinion regarding the correct approach to the problem of vaginal aplasia.

The comments made in this report are based on an analysis of 32 cases of congenital absence of the vagina seen in the Department of Gynecology at the Johns Hopkins Hospital. In all 32 patients a vagina was constructed by the method of Sir Archibald McIndoe. The first vagina constructed by this method at the Johns Hopkins Hospital was done Nov. 16, 1943. The last one was done on June 26, 1956.

Embryology

Embryologically, the vagina is now thought to arise from a fusion of the Müllerian ducts in the midline above and from the urogenital sinus below. Almost the entire vagina is thought to be derived from the fused Müllerian ducts; perhaps only the lower sixth is formed from the urogenital sinus. The stratified squamous epithelium of the urogenital sinus invades the Müllerian canals, and proliferation of the squamous epithelium produces a solid epithelial cord. It is the later desquamation of the cells in the center of this cord which forms the vaginal canal. The canal first begins to make its appearance in 150 to 200 millimeter embryos. 10, 26

Absence of a vagina results from an embryological arrest in the development of the lower portion of the Müllerian system. This produces, consequently, not only an absence of the vagina, but usually an absence of the uterine fundus and cervix as well, since the uterus is also derived from the Müllerian ducts. The ovaries are normal since their origin is from quite a different source. Rudimentary Fallopian tubes may be present and these may end in small bulbous dilatations on each side of the midline behind the bladder. These bulbous dilatations may contain functioning endometrium, and a hematosalpinx may occasionally result. Wharton reports that one patient developed rather large myomas in these rudimentary structures.²⁶

Externally, just within the hymen there may be a shallow vaginal vestibule extending from 1 to 2 cm. This is the part of the vagina which is formed by the urogenital sinus. The urogenital sinus is not defective in these patients.

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As indicated above, the ovaries are invariably present, and they function normally as indicated by the development of normal female secondary sex characteristics. The external genitals, pubic hair, and breasts develop normally, and the body contour and mental attitudes are entirely feminine. In rare instances, congenital absence of the vagina may be associated with hermaphroditism. When it occurs in male pseudohermaphrodites, the ovaries are absent and the gonads are testes. The Müllerian ducts may be absent, but the external genitals may resemble the female type. In this situation, of course, female secondary sex characteristics will not develop.

Infrequently, the portion of the Müllerian system which is responsible for uterine development is not defective and the uterine cervix empties into a small cavity above the congenitally absent vagina. In 2 of the 32 patients in the present series the uterus was present. In one patient, a laparotomy was performed in another hospital eight years prior to the construction of the vagina. The details of the first operation are not known, but it is thought to have been a hysterectomy for a hematometra. In another patient, aged 15 years, a cervix and normal-sized uterine fundus were present at operation, and a small amount of old blood was released when the dissection reached the external cervical os. In a series of cases of congenital absence of the vagina reported from the Mayo Clinic in 1949, 26 patients were subjected to pelvic operations permitting visualization of the internal female genitals. Only 4 of the 26 patients had a normal uterus. Six patients were found to have infantile uteri and one patient a bicornuate uterus.

Patients with congenital absence of the vagina and a normal uterus may conceive after construction of an artificial vagina. Several examples are recorded in the literature.^{1, 18, 21, 28} These patients have usually been delivered by cesarean section at term without a trial of labor. Presumably this is because the artificially constructed vagina will not allow the stretching necessary for vaginal delivery. There have been no pregnancies in the present series. One of us (L. R. W.), however, has performed a plastic operation on a patient with congenital absence of the lower half of the vagina. The original operation was done at the age of 13 because of cryptomenorrhea. Vaginal scar tissue was excised at the age of 22 just before marriage. Two years later the patient became pregnant and was delivered vaginally at term. Also, one of us (R. W. T.) has performed a plastic operation on a patient with congenital absence of the middle third of the vagina. This patient became pregnant, and her obstetrician elected to deliver her at term by cesarean section.*

Associated Anomalies of the Urinary Tract

The association of congenital anomalies of the upper urinary tract with congenital absence of the vagina has been emphasized by previous writers. This association is not hard to understand when one remembers that in early embryological life the urogenital fold is the anlage of important parts of both the genital and urinary systems. These anomalies of the urinary system always involve the upper urinary tract, that is, the kidneys and ureters, since the urethra and bladder are not derived from the urogenital fold.

Phelan, Counseller, and Greene¹⁵ have emphasized the importance of these associated urological anomalies. In 72 patients with vaginal agenesis who were investigated, one-fourth of the total group were found to have significant urological anomalies. Those of most frequent occurrence were renal ectopia and renal agenesis. A urological investigation is necessary before construction of an artificial vagina. A pelvic kidney or an abnormally placed ureter could

^{*}This patient's anomaly and its correction are illustrated in Fig. 348 of Te Linde.20

easily be injured if it interfered with the dissection of a vaginal space of adequate width and depth. It would indeed be doubly unfortunate if the injured kidney or ureter represented the patient's only kidney or ureter. The patient with vaginal agenesis and a pelvic mass should always be investigated urologically to rule out the presence of a pelvic kidney before laparotomy is resorted to to explain the nature of the mass.

In the present series, 17 patients were studied urologically and 8 were found to have major congenital urinary tract anomalies. These are listed in Table I. Minor anomalies of the renal collecting system and minor anomalies of bone (spina bifida) were also found.

TABLE I. CONGENITAL ANOMALIES OF THE URINARY TRACT ASSOCIATED WITH CONGENITAL ABSENCE OF THE VAGINA

17	patients	studied	urologically	

- 8 major urological anomalies found
 - 2 absence of left kidney with normal right kidney
 - 1 single pelvic kidney

 - 1 right pelvic kidney with normal left kidney
 1 crossed ectopia of left kidney with normal right kidney
 1 crossed ectopia with fusion of both kidneys on left, none on right
 - 1 left ectopic kidney with normal right kidney
 - 1 bilateral ureteropelvic junction obstruction with right staghorn calculus and saccular left renal pelvis

Indications for Construction of an Artificial Vagina

There are three different types of cases in which the construction of an artificial vagina is considered advisable. First is the rare case of an absent vagina and a normally functioning uterus. In this situation the construction of an artificial vagina is necessary in order to allow an exit for the menstrual flow.

Second, the patient who is married or is making plans for marriage should have a vagina constructed. Of the 32 patients in the present series, 10 were married and complained of inability to have satisfactory coitus. In an additional 9 patients marriage was being considered within a year after the operation was done. Construction of a vagina in these patients is justifiable in preparation for matrimony.

Thirteen patients were single and had no plans for marriage at the time the operation was done. These patients presented with the complaint of primary amenorrhea. The operation was indicated in these patients to minimize the psychological trauma associated with the knowledge of a congenital deformity of the genitals.

There seems to be no argument about the first two indications just mentioned but the third indication, that of minimizing psychological trauma, is open to some question. It is thought by some that there are no valid reasons why a young girl with congenital vaginal aplasia should not receive the benefit of modern surgical correction, and at a sufficiently early age to help in her adjustment. If the patient is intelligent and cooperative, she can be taught to use a comfortable form to keep the vagina open until she is married. Opponents of this reasoning advocate delaying the operation until a few months before marriage so there will be no tendency for the newly formed organ to become constricted from lack of use. As we shall see, the best results are obtained when the vagina is not allowed to become constricted after the first operation. The first operation has the best chance for success; subsequent operations to open up a constricted artificial vagina are often unsuccessful. One way to insure success is to construct the vagina initially about six months before the patient is to be married. Much of the psychological trauma comes from the lack of menstruation, and this cannot be relieved by constructing a vagina in a patient who also has a congenital absence of the uterus. In spite of these objections, however, it may be wise in some instances to proceed with the operation before the patient has any marriage prospects even though the possibility of ultimate success is somewhat lower.

Methods of Constructing an Artificial Vagina

A review of the methods devised for the formation of an artificial vagina is given in Table II.

TABLE II. SOME METHODS OF CONSTRUCTING AN ARTIFICIAL VAGINA

Nonsurgical	·—
	1. Simple pressure (Frank, 1938)
Surgical.—	
	1. Intestinal transplantation
	a. Small intestine (Baldwin, 3 1907)
	b. Rectum (Popoff, 16 1910, Schubert, 17 1911)
	2. Pednuculated flaps
	a. Simple labial and thigh flaps (Graves, 8 1921)
	b. Tubed pedicle flap from thigh (Frank and Geist, 1927)
	3. Simple reconstruction with insertion of form (Wharton, 23 1938)
	4. Simple reconstruction with insertion of inlay graft over form

First of all, a nonsurgical approach to the problem was advocated by Frank in 1938. This method consists of intermittent pressure made by a mold just below the external urethral meatus. Successful examples have been reported by Frank, 5, 6 by Holmes and Williams, 9 and by Marshall. 11 Others agree, however, that this method is either a complete failure in most cases, or it results in a vagina of inadequate depth and caliber. The patient performs these dilatations herself, and if the delicate mucous membrane is ever traumatized, subsequent dilatations are painful and become difficult because of the formation of scar tissue. The Frank procedure was used as the primary treatment in 3 of the 32 patients in this series. It failed in all 3. In our experience, the Frank method has been partially successful in only one case. In this patient the vagina formed was small but apparently satisfactory for coitus for the patient and her husband, so a surgical procedure was not recommended. We have discarded the nonsurgical approach in favor of the surer and more satisfactory surgical approach which is now available.

Steinmetz,¹⁹ Marshall,¹¹ and Miller, Willson, and Collins¹⁴ have reviewed the historical aspects of our subject. Reports of the operative correction of vaginal aplasia before the beginning of the present century are scanty. But in 1904, James F. Baldwin² of Columbus, Ohio, suggested the possibility of utilizing a double loop of ileum or sigmoid to line a space dissected between the rectum and the bladder, leaving the mesentery connected to the bowel. The continuity of the intestinal tract was to be re-established by an end-to-end anastomosis. In 1907 he³ reported the first case of operation by this method, with the use of a loop of ileum. He reported that the resulting vagina was absolutely normal in every way. In 1910 Popoff¹¹⁶ constructed an artificial vagina utilizing a portion of the rectum which was moved anteriorly. This operation was modified by Schubert¹¹† in 1911. The rectum was severed above

the anal sphincter and moved anteriorly to serve as the vagina. The coccyx was resected posteriorly to allow room for the sigmoid to be sutured to the anus, and the continuity of the intestinal tract was thus re-established.

Competition developed between these two operations. The Schubert-Popoff operation was more popular, particularly in the European clinics. The report of a patient who had a vagina constructed by this method and subsequently gave birth to three children enhanced its popularity.²¹ The mortality rate for the Baldwin operation was recorded at 17 per cent and for the Schubert-Popoff operation at 3.2 per cent.¹⁴ The high mortality and morbidity of both operations were a sobering influence and their popularity declined. Occasional prolapses of the intestinal segments and excessive irritating discharge from the intestinal glands were additional disadvantages. These operations have now been completely abandoned in this country, although the older gynecologists say that the anatomical and functional results were quite good. An occasional report of their use still can be found in the medical literature from continental Europe and Russia.

Attention was then directed to less formidable procedures, consisting of dissection of an adequate space between the rectum and bladder and lining this space with flaps of skin. Graves,^{\$\$} in 1921, lined the space with four pedicled flaps, two from the labia and two from the inner thigh. Frank and Geist,⁷ in 1927, modified this with an application of the Gillies tubed pedicle, with better results. But the pedicle had to be rotated through 180 degrees to reach the apex of the new vaginal space and because of this the pedicle could easily undergo necrosis at its base. Also the operation had to be done in several stages and resulted in marked scarring of the thighs. Hair usually grew in the vagina because of the transplantation of skin appendages. Extensive plastic procedures are no longer necessary or desirable to construct a vagina and consequently these two operations have been discarded. They did serve the purpose of placing emphasis on the use of safer procedures.

Simple reconstruction procedures began to take the place of the more formidable plastic operations. Wharton²³ in 1938 was the first to emphasize two of the three important principles which are used today in construction of an artificial vagina. He combined an adequate dissection of the vaginal space with continuous dilatation by a balsa-wood form covered with a rubber sheath and left in the space. In 1940, Wharton²⁴ reported 12 examples of vaginas constructed by this method with good results in 10 cases. The first operation was performed in 1928. The operation is based on the principle that the vaginal epithelium has remarkable powers of proliferation and in a relatively short time will cover a raw surface. A similar process occurs in the fetus when the epithelium of the urogenital sinus forms the vaginal canal. Wharton merely applied this principle in the adult. This simple procedure is entirely satisfactory as long as the space is kept dilated for a sufficient time to allow the epithelium to grow in. But occasionally even after several years the vault of the vagina remains without epithelial covering. Coital bleeding and leukorrhea result from the persistent granulation tissue and there is a tendency for vaginas constructed by this method to be constricted from scarring in the upper portion.

It is of interest that as recently as 1949 in the Mayo Clinic report⁴ of construction of 100 vaginas, 14 were done by Wharton's method. The authors concluded that this simple reconstruction with insertion of a form gave excellent results in all 14 cases. They stated that they had not noticed that the disadvantage of persistent granulation tissue with bleeding and leukorrhea was of any consequence. This has not been our experience.

In 4 of the patients in the present series a previous attempt to form a vagina by Wharton's method was unsuccessful. In one case the vagina was constructed in 1943 by simple dissection of a space and insertion of a form. The vagina epithelized except for a 3 cm. area in the vault. Finally there was severe constriction in the vault, and the granulation tissue persisted until 1947. A satisfactory vagina was formed only after redissection of the space and application of an inlay graft over a form.

When inlay grafts were first used to construct an artificial vagina the results were poor because the necessity for dilatation of the new vagina was not recognized. Severe contraction, uncontrolled by continuous or intermittent dilatation, almost invariably spoiled the results. It remained for Sir Archibald McIndoe¹³ at the Queen Victoria Hospital in England in 1938 to combine the three principles used today in the operation for vaginal agenesis. These principles are: first, dissection of an adequate space between the rectum and the bladder; second, inlay grafting; and third, the cardinal principle of continuous and prolonged dilatation during the contractile phase of healing.

He also emphasized the important features of inlay grafting:

1. The eavity must be prepared with care. The walls must be smooth, clean, and healthy, and there must be no nonviable tags which could not receive a graft.

2. Hemostasis and asepsis must be absolute. Separation of the graft from its bed by blood, serum, or pus means the inevitable death of the graft over that area.

3. The graft must be applied to the dissected space over a form, with even pressure exerted over the whole surface of the graft.

4. The graft itself must be as thin as possible. Theoretically, only the epidermis should be used so that skin appendages such as hair follicles, sweat glands, and sebaceous glands are not transferred to the vagina.

5. Under no circumstances must the form be left out of the vaginal cavity for more than a few minutes at a time until all tendency to constriction has ceased. Inlay grafts in the body cavities suffer from this contractile phase more severely than any other type of free graft. A graft, once contracted, never expands, and cannot be made to do so by mechanical means.^{12, 13}

The method used by us is essentially the one described by McIndoe and Bannister. The graft is usually taken from the superomedial aspect of the thigh. Because of the possibility of leaving a visible scar, a few patients have requested that the graft be taken from the hip or the buttock. These latter sites are not as easy to handle in the postoperative period. The Reese dermatome is a convenient instrument to use in taking the graft. The graft is taken first and laid aside in a saline-moistened sponge. After the space is dissected and hemostasis secured, the graft is sutured around a balsa-wood form previously covered with two rubber sheaths. We prefer balsa-wood forms because they may be safely sterilized, they may be shaped at the operating table to fill the vaginal space and accommodate the urethra, and they are light for the patient to wear. The edges of the graft are sutured to the edges of the vaginal mucosa at the vestibule of the vagina. After two weeks the form is removed, the new vagina inspected, and the form reinserted. The patient is then taught to remove and reinsert the form.20, 27

Two points in technique deserve emphasis. During dissection of the space there is danger of injuring the urethra, the bladder, or the rectum. This is more apt to occur in the presence of scar tissue from a previous attempt at construction of a vagina. To facilitate dissection in the right place, a Hegar dilator is usually placed in the urethra, and an assistant is asked to place his finger in the rectum. This will help prevent injury to these structures.

A shallow groove must be made in the form to accommodate the urethra. If this is not done the constant pressure of the form on the urethra may cause ischemia with sloughing of the distal end.

Before the operation begins, it is important to distinguish between a congenitally absent vagina and uterus, and cryptomenorrhea resulting from an imperforate hymen. Usually this can be done by a pelvic examination. When the vagina and uterus are congenitally absent, on rectal examination the urethra can be easily felt through the anterior rectal wall. This will be even more striking if an instrument is placed in the urethra while the rectal examination is made. On the other hand, if one is dealing with an imperforate hymen with the vagina and uterus present, a large distended hematocolpos will be felt between the urethra and the rectum, and the instrument placed in the urethra will not be easy to feel.

Results

The functional result is more important than the anatomical result in evaluating the success of the operation. A vagina only 6 cm. long may be adequate for satisfactory coitus.

Follow-up is not available on 3 of the 32 patients in this series. Of the remaining 29 patients, the result must be classed as unsatisfactory either anatomically or functionally in 5. In one of these 5 it was necessary to remove the form on the fourth postoperative day because of vaginal bleeding. The vaginal vault constricted but was subsequently lengthened with another operation. In another patient a small rectovaginal fistula developed which healed spontaneously in a short period of time. Although the functional result was satisfactory according to the patient, the vagina was only 4 cm. long but normal in caliber. In the other 3 unsatisfactory results, the patients did not wear the forms as instructed; 2 of these patients were unmarried.

In addition to these complications, two other rectovaginal fistulas occurred. Both were repaired leaving vaginas of excellent size. In 2 patients there was some sloughing of the distal urethra as a result of pressure of the form. These patients remained entirely continent of urine and it was not necessary to repair the urethra. Except for 3 rectovaginal fistulas, 2 urethral sloughs, and one postoperative hemorrhage, there were no other serious complications. One patient developed a constriction ring at the outlet which was simply incised and the ultimate result was excellent. One patient discovered on her honeymoon that the vagina was too large. This was corrected by a simple posterior repair.

In 26 patients who have been followed for more than a year after construction of an artificial vagina, the final result can be classed as satisfactory in 21 cases, or 81 per cent.

Summary and Conclusions

- 1. Experience with the McIndoe operation in 32 cases of congenital absence of the vagina indicates that a successful result was obtained in approximately 81 per cent.
- 2. The McIndoe operation is a safe, efficient method of constructing an artificial vagina, and is the operation of choice provided the three cardinal principles are strictly adhered to, namely, dissection of an adequate vaginal

space with good hemostasis, proper application of an inlay graft, and continuous dilatation until there is no tendency of the new vagina to become constricted.

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INTERFERENCE MICROSCOPY IN THE STUDY OF **HUMAN ENDOMETRIUM***†

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MPORTANT new contributions to the study and analysis of cellular structure and function are appearing from the fields of physics and chemistry. 13 For some years we have been surveying these methods for potential relevance to problems of growth in human female genitals. When a new method of cell study seems likely to reveal important information in this area, the technique has been applied to human material, after adaptations.8, 9, 10 Such a new method is cell refractometry, employing the interference contrast microscope.

Interferometry³ has been used for many years to measure the refractive indices of substances, especially liquids and gases, and is capable of great sensitivity and accuracy. It is only in recent years that high-performance interference microscopes have been constructed. Interference microscopy and phase contrast both provide images by means of optical interference phenomena, but interference microscopy is not dependent on diffraction by the object The interfering beams which produce the contrast are generated by an interferometer system incorporated into the microscope itself. permits contrast for features, with phase changes too gradual for phase contrast microscopy. The image brings out the general morphology of the specimen better than phase contrast microscopy and bears more resemblance to that obtained by staining methods. Precise measurements can be made of the amount of phase change produced. This phase change is dependent in part on mass, which is largely a function of protein content in most cells.

This new method of quantitation of certain cell properties has considerable potentiality. As cytologists we speak in rough approximations of hyperchromatism, nuclear cytoplasmic ratio, nucleolar size, and cytoplasmic baso-Therefore any method which facilitates quantitation of cell mass and protein content must be of interest to us on a research basis.

In the present study, as a first entry into the field of interference contrast microscopy, we have attempted measurements of nuclear refraction on 120 examples of human endometrium. No striking and characteristic findings in nuclear refractive properties appeared among the various patterns of endometrium.

^{*}This investigation was supported by grants from the Damon Runyon Memorial Fund (DRG-352) and the National Cancer Institute, Public Health Service (C-2719). †Presented at the Session on New Advances in Cytology, International Cancer Cytology Congress, Chicago, Oct. 11, 1956.

Materials and Methods

One hundred and twenty specimens of endometrium were studied. These were consecutive specimens arriving in the laboratory, except that some with insufficient material were not employed. All were derived from uterine curettage. Direct impression smears were made from all specimens. These were immediately fixed in ether-alcohol. One smear from each case was subjected to the Papanicolaou stain. Another was left unstained but was passed through the same organic solvents as in Papanicolaou's method and mounted. H.S.R.* mounting medium was employed, having a refractive index of 1.54 (at 18° C.). Corning Glass Works No. 1 Thinness microscopic cover glasses (0.13 to 0.17 mm. in thickness) were employed.

The tissue specimens were fixed in neutralized formalin and dehydrated in an automatic tissue processing machine in the following routine: formalin (4 hours), 70 per cent alcohol (1 hour), 95 per cent alcohol (2 hours), absolute alcohol (1 hour), acetone (2 hours), xylol (2 hours), paraffin (3 hours) and blocked in Tissuemat.† Sections were cut at 5 μ . One or more sections from each block were stained with a standard hematoxylin and eosin routine for diagnosis and for control of the interference contrast microscopic studies. Consecutive sections from the same blocks were deparaffinized in the oven and in xylol. The sections were mounted in H.S.R. mounting medium and Corning No. 1 cover glasses applied. Tissue diagnoses were established according to generally accepted criteria.14

The unstained sections and smears were studied with a Baker Interference Microscope. A Zeiss-Winkel Standard combination monocular-binocular tube was substituted to permit photomicrography during primary examination. An Ortho-Illuminator B. was employed as a light source, with a 300 watt incandescent bulb. Kohler illumination was employed. All examinations were performed with the double-focus system, with the 40× objective.

The routine for examination of sections was as follows:

1. A characteristic area of endometrium was located.

2. A Baker green didymium filter (a broad band filter centering on 586 $m\mu$) was inserted below the stop tray.

3. Readings were taken with the goniometer analyzer, based on the appearance of the nuclei of glandular epithelium. All other structures in the field were neglected for the purpose of this study. The reference points were areas of no tissue, principally empty gland lumina.

4. Individual readings in each microscopic field were taken as follows:

ND: One reading was taken in the condition of nucleus dark (positive contrast) with the nuclear chromatin particles as dark as possible in contrast to the light reference area (Fig. 1, A).

I: The second reading was taken at invisibility, with the reference

area and the nuclear chromatin indistinguishable.

NL: The third reading was taken in the condition of nucleus light, (negative contrast) with the nuclear chromatin particles as light as possible in contrast to the dark reference area (Fig. 1, B).

5. Readings from 10 microscopic fields were taken according to this routine.

6. The mean differences between the goniometer analysis readings (in degrees) obtained in the conditions of nucleus dark and invisibility (ND-I),

†Fisher Scientific Co.

^{*}H.S.R.—Harleco Synthetic Resin, a product of the Hartman-Leddon Co., 5821 Market St., Philadelphia 39, Pa.

nucleus light and invisibility (NL-I), and nucleus dark and nucleus light (ND-NL) in the ten areas from each case were recorded. The direct impression smears were similarly examined.

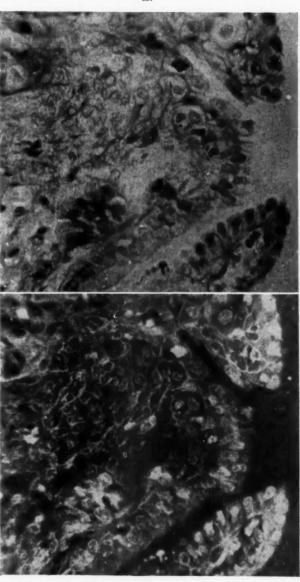


Fig. 1.—A, Endometrium in early pregnancy, unstained section as seen in positive contrast in the interference microscope. (×372; reduced ½.)

B, Same field as A, with analyzer of interference microscope set for negative contrast. The difference between the analyzer dial readings for positive and negative contrast represents one half the fractional part of a wave length, expressed in degrees, by which the nuclei changed the phase relative to the clear zone of no tissue, serving as the reference area. (×372; reduced ½.)

Results

The number of cases in each category of tissue diagnosis and the mean differences in degrees obtained between the conditions of nucleus dark, invisibility, and nucleus light in the tissue sections are recorded in Table I and diagrammed in Fig. 2. Twice the difference between the conditions of nucleus dark and nucleus light (C) should be the fractional part of a wave length, expressed in degrees, by which the nuclei changed the phase relative to the area of no tissue. The differences between nucleus dark and invisibility (A), and nucleus light and invisibility (B) should be approximately equal. Each should represent one fourth the fractional part of a wave length, expressed in degrees, by which the nuclei changed the phase relative to the reference area.

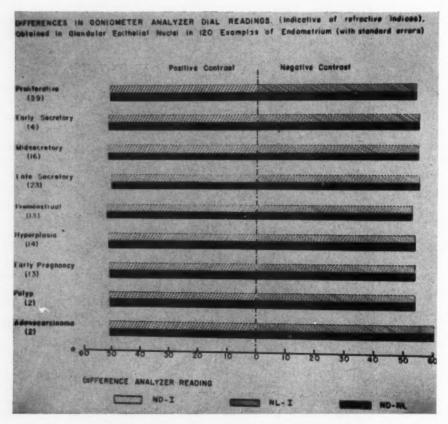


Fig. 2.—The differences in analyzer dial readings diagrammed are indicative of the phase change induced by the endometrial nuclei. Essentially similar findings occurred in the various endometrial patterns except for the slightly higher value obtained in adenocarcinoma. The figures in parentheses denote the number of cases of each type examined.

Statistical comparisons among the values obtained in the various endometrial patterns were made with the "t" test. 7, 16 In every endometrial pattern where more than one case was represented, the values obtained for the conditions nucleus dark to invisibility (Table I, A), nucleus light to invisibility (B), and nucleus dark to nucleus light (C) were compared with all other endometrial patterns. In only one instance was marked difference found. In computing the series nucleus light to invisibility (C), endometrial adenocarcinoma gave higher values than did proliferative endometrium (C) = 2.99, 0.01 > C0.001).

In only one third of the cases were the cells in the ether-alcohol-fixed smears sufficiently discernible with the interference microscope to permit analyzer readings. The data from these will not be discussed further, but the reason for the failure will be noted below.

Table I. Differences in Goniometer Analyzer Dial Readings (Indicative of Refractive Indices) Obtained in Glandular Epithelial Nuclei in 120 Examples of Endometrium (With Standard Errors)

TISSUE TYPE AND NUMBER OF CASES IN EACH*	A DEGREES CHANGE IN READING FROM POSITIVE CONTRAST (NUCLEUS DARK) TO INVISIBILITY (ND-I)	B DEGREES CHANGE IN READING FROM NEGA- TIVE CONTRAST (NUCLEUS LIGHT) TO INVISIBILITY (NL-I)	DEGREES CHANGE IN READING FROM POSITIVE CONTRAST (NUCLEUS DARK) TO NEGATIVE CONTRAST (NUCLEUS LIGHT) (ND-NL)
Proliferative 39 cases	52.3 ± 0.9	56.3 ± 0.9	108.6 ± 1.4
Early secretory 4 cases	53.3 ± 1.6	58.4 ± 1.6	111.7 ± 2.9
Midsecretory 16 cases	53.6 ± 1.0	58.4 ± 0.9	112.0 ± 1.7
Late secretory 23 cases	51.9 ± 0.7	59.0 ± 0.8	110.9 ± 1.4
Premenstrual 3 cases	54.2 ± 2.1	54.2 ± 2.8	. 108.4 ± 3.4
Hyperplasia 14 cases	52.9 ± 1.00	56.8 ± 1.5	109.7 ± 2.1
Early pregnancy 13 cases	51.9 ± 1.2	57.0 ± 1.5	108.9 ± 1.6
Polyp 2 cases	51.8 ± 1.5	57.2 ± 3.00	109.0 ± 5.6
Adenocarcinoma – 2 cases	52.0 ± 5.0	60.7 ± 1.2	112.7 ± 6.2

^{*}Also 1 case of atrophic endometrium, menstrual phase endometrium, lower uterine segment endometrium, endometrium with chronic inflammation.

In the double-focus system used in this study two images are created, one a little above the other vertically, by a combination of special lenses including a birefringent quarter-wave plate. The relationship between two pieces of polaroid, one below the substage, and one below the eyepieces, determines the color pattern and intensities in the single image seen. Readings (in degrees) are taken from a dial which indicates the relationship of the two portions of polaroid. In going from the condition of nucleus dark (positive contrast, Fig. 1, A) to nucleus light (negative contrast, Fig. 1, B) as we did, using the clear zone of no tissue as reference area, twice the angle through which the analyzer is rotated from the first to the second position is the fractional part of a wave length (expressed in degrees) by which the nuclei changed the phase relative to the clear zones. We also recorded the intermediate reading, when the nuclei and the reference area matched. Here, in fact, the nuclei were invisible. The change in dial reading from nucleus dark to invisibility, or from nucleus light to invisibility is said to be one fourth the phase change produced by the nuclei. Table I readily shows, however, that the change in reading from nucleus dark to invisibility (A) was not exactly the same as that from nucleus light to invisibility (B). The actual end point at either nucleus dark or nucleus light was not sharp. Moving the dial 5 degrees did not produce marked changes. The end point was not markedly different for certain different structures in the same field, some of which seemed to have greater refractivity than others. The end point at invisibility was quite sharp, however, and a few degrees' rotation of the dial made a marked difference. Here the end point at invisibility differed among different nuclei in the same field, and the recorded reading was that of the majority of nuclei. Clarification of these points will await further study, not only by ourselves, but by scientists doing more basic research on the theory and application of the instrument.

Comment

In the first application of a new experimental method, problems of validity of results are paramount. Since we have made certain adaptations to our purposes, and are employing the instrument in a manner somewhat different from that described in available literature, we must be particularly cautious in matters of interpretation. There are two interpretations of our almost complete failure to obtain statistically significant differences in the readings derived from different patterns of endometrium:

- 1. That no significant path differences (the product of refractive index and thickness¹⁵) occurred in the nuclei in the various endometrial patterns.
- 2. That our methods were not adequate to reveal differences that may have been present, and that any minor differences occurring from case to case depended on artifacts.

We cannot make a definite choice of these alternatives, but it is our opinion that we have adhered to the principles of interference microscopy, and that our method should have demonstrated significant differences, if present. It seems wiser not to dwell upon the difference noted between adenocarcinoma and proliferative endometrium, since we had only two examples of the neoplasm. Further experience must clarify this point. It may well be that we could have devised a technique which would have given more accurate readings in individual cases. However, this would have been opposed to a general plan on which we have been working for several years. This is to do our special histochemical and other studies on preparations conforming as closely as possible to those on which practical tissue diagnoses are made.^{8, 9, 10} In this way our results might have optimum meaning as far as practical implications are concerned.

It is difficult to find suitable publications on human endometrium for comparison with our results. Harkin¹¹ studied 8 specimens of endometrium (2 proliferative, 3 secretory, 3 atrophic) by Feulgen microspectrophotometry for nuclear desoxyribonucleic acid (DNA). He found differences among the three groups, and concluded that the nuclei of endometrial glands have a nearly constant DNA value, and that higher values obtained during the proliferative phase are a reflection of DNA synthesis during interphase. The reaction of DNA to certain stains is in part dependent on polymerization.12 Therefore changes in DNA need not be accompanied by changes in nuclear mass. Our present interference contrast microscopy is based on mass only, and not upon arrangements of the molecules present. Nucleoproteins result from the combination of nucleic acids and proteins, and in certain cells constitute the major portion of the solid material.6 Swift17 stated that amounts of DNA in nuclei are remarkably stable in the presence of physiological changes which may cause alteration in nuclear volume and cell activity. It is reasonable to assume that this thought process may be reversed, to suppose that changes in DNA in the nucleus may not necessarily be accompanied by changes in total protein content. It is probably not necessary to consider

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lipids and carbohydrates as contributing significantly to nuclear mass in the sections we examined. Even in living cells examined by refractometry⁴ the presence of protein derivatives, lipids, carbohydrates, and salts was considered unlikely to affect the refractive index of the cells to any great extent. Our methods of fixation and dehydration probably removed all but traces of such nonprotein constituents of the nuclei.

In this study we have not taken advantage of one of the greatest potentialities of the interference contrast microscope, since with it refractive indices can be determined upon living cells.⁵ As indicated previously, our first study was planned to use material as near as possible to routine diagnostic sections. Then, too, usually some modifications are necessary in adapting methods in use by biological scientists to the study of human tissue in a hospital pathology laboratory. Pathologists rarely have much control over the arrival time, quantity, and type of tissue of their specimens. As a matter of practical logistics and patient service, tissue specimens in a hospital laboratory must undergo some initial preparation, and a tissue diagnosis must be returned as soon as possible to the clinician. The investigations must be accomplished in interstices of time between service and educational duties. As long as basic principles of technique are adhered to, however, information of value can be obtained by these attempts to bridge the gap between pure research and pure service laboratories.

We probably made our task more difficult by employing a mounting medium with a refractive index (1.54) approximating that of fixed tissue. Doubtless it was for this reason that so many of the ether-alcohol-fixed impression smears were not visible to the interference contrast microscope. We were concerned about the validity of results from these smears for another reason, however. In the Papanicolaou-stained smears the cells consisted almost solely of nuclei, with little or no cytoplasm visible. We could not be certain which nuclei derived from glandular epithelium, and which from stroma.

We have not attempted comment on exact nuclear mass. To do so we would have to determine nuclear volume, and to have more accurate indication of section thickness. Path difference (of which our measurements were a function) is the product of refractive index and thickness. In this initial study our sights have been deliberately set low. We wish only to compare certain optical properties of endometrial epithelial nuclei indicative of protein content.

There can be little doubt that the interference contrast microscope is a tool of great potential in our field of investigation. There will be technical improvement. Scientists will contribute further to the theory of the instrument and to the meaning of the findings obtained from living and fixed cells. Based upon these advances, judicious application of the instrument to human material should add to our understanding of normal and physiological growth. We plan next a study of cervical squamous epithelium; normal, metaplastic,

atypical hyperplastic, intraepithelial carcinomatous, and invasive carcinomatous. By employing two different mounting media, one with refractive index greater than fixed tissue, and one with lower refractive index, we hope to be able to derive more exact information about the cells.

Summary

Interference contrast microscopy, a new method of cell refractometry, has been applied to glandular epithelial nuclei in 120 examples of human endometrium. This technique reflects the protein content of the nuclei. Except for a slightly higher value in adenocarcinoma than in proliferative endometrium, no striking differences were found. The limitations and potentialities of the instrument in the study of the growth process in human female genitals have been discussed.

The technical assistance of Miss Gladys Clark is gratefully acknowledged.

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CINERADIOGRAPHY OF FEMALE PELVIC ORGANS

A Preliminary Report on a New Method

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CINERADIOGRAPHY of female pelvic organs is a new kind of hysterosalpingography. The original method of hysterosalpingography has been continuously improved since 1914 when it was introduced by Rubin, 1 Cary, 2 Dartigues and Dimier. 3 The contrast media used for injection are safer today, the speculum is made of nonopaque material; serial pictures of filling and evacuation, introduced by Hyams 4 and Dalsace, 5 have replaced the former single roentgenogram; finally, today's practice of taking roentgenograms in a variety of positions constitutes a definite progress.

Another modification of the original method is the combined use of hysterosalpingography and fluoroscopy. Opinion is divided, however, on whether the additional information that fluoroscopy may furnish is really worth the risk incurred by the patient through longer radiation exposure of the genital area.

The new method of "movie hysterosalpingography" with continuous simultaneous full-size visualization (referred to as "cineradiography" in this paper) appears to constitute a great progress in its application to gynecological diagnosis.

We knew of the pioneer work of Porsche and Varangot⁶ in this field, but developed a somewhat different technique. This cineradiographic film was presented for the first time at the Second World Congress on Fertility and Sterility in Naples, Italy, in May, 1956.⁷ In June, 1956, the American Journal of Obstetrics and Gynecology published Stevenson's article on the same subject. This paper disclosed that Stevenson had shown a movie on cineradiography as early as 1954, a fact of which we had had no previous knowledge.

Technique

The equipment utilized in our studies consisted essentially of: (1) a freely movable radiographic stretcher; (2) an x-ray source with fractional focal point; (3) an electronic image intensifier tube; (4) an optical system permitting visualization without dark adaptation, both during recording and during fluoroscopy; (5) a standard 16 mm. motor-driven motion picture camera (Fig. 1).

In order to obtain films with good resolution, a fractional focal-point roentgenographic tube was chosen. This is a tube with a very small (0.35 mm.) gap from which the x-rays emanate. The relatively low dosages required for these studies permit exposures of adequate duration without danger

of overloading the x-ray tube. Conventional filtration is used.

The tube is fitted with an additional lead diaphragm which limits x-radiation to the 5 inch circular area of the image intensifier, minimizing scatter and stray radiation. The roentgen rays produced by the fractional focal-point tube, after passing through the patient, impinge on a fluoroscopic screen within the intensifier tube. By means of both electron acceleration and electron-optical demagnification an image of greatly increased brightness is produced at the viewing point of the image intensifier tube. The optical system which receives this intensified image permits recording of the image by the 16 mm. motion picture camera, as well as simultaneous observation of a full-sized image without dark adaptation. The target skin distance is 30 inches.

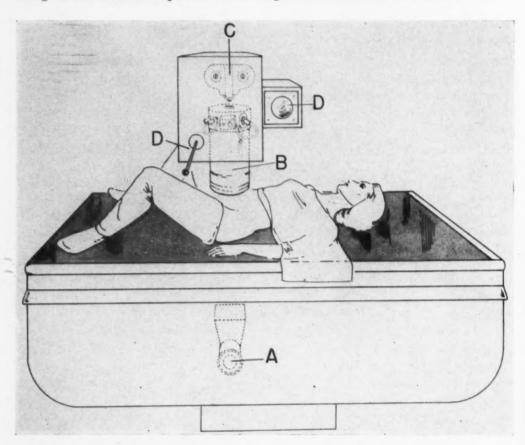


Fig. 1.-A, X-ray source. B, Image intensifier. C, Camera. D, Viewing system.

The roentgen exposure for this procedure is well within safe limits. Utilizing a Lysholm grid (2×) the average skin dose was 6 r per minute of recording. The film studies were recorded at a rate of 8 frames per second on a medium-speed, reversible 16 mm. film (40 Weston). The actual factors used were 4 Ma. and 90 KVP. during recording.

It should be stressed that, because of a higher brightness level, sharper contrast and better detail perception are possible, Also, the need for dark

adaptation is completely eliminated.

Some workers in this field prefer 35 mm. film for recording. There are many reasons in favor of the 16 mm. system, however, such as greater economy in operation, simplicity of handling, and reduced x-ray dosage. The use of 16 mm, film was not found a deterrent to good definition. In all cases the

resolving power of the 16 mm. emulsions and of the optics used was higher than that of the intensifying screen. It became apparent that actually the grain size of the intensifying screen was the limiting factor.

At the present time, only a circular area 5 inches in diameter is engulfed by the image intensifier tubes. Some investigators consider this a disadvantage, but in our view a freely movable suspension system will offset this handicap. The image intensifier-camera unit used by us was rigid, but the patient,

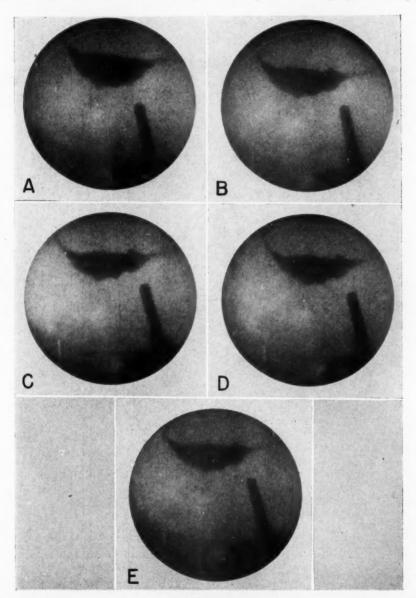


Fig. 2.—A 31-year-old woman with irregular menses. Menometrorrhagia for 4 weeks. Cytology smear shows no malignancy. Hysterography with Salpix. A ,B, C, D, E, Frames taken from cineradiograph demonstrating waves along wall of the fundus.

on a freely movable x-ray stretcher, could be moved into any desired position. It should be remembered that the larger the area to be recorded, the smaller are the images on the film and the less detail can be resolved.

Fig

Comparison With Hysterosalpingography

Cineradiography offers the following advantages:

- 1. The time required for examination is considerably shorter. As the x-ray study can be completed within 2 to 3 minutes the patient suffers less discomfort.
- 2. An x-ray movie of the uterus and tubes is taken under simultaneous fluoroscopic visualization. Thus, the patient may benefit from the advantages of fluoroscopy without the necessity of being exposed to additional radiation and with the possibility of injecting only a minimum quantity of contrast medium.
- 3. Unlike fluoroscopy, cineradiography provides a permanent record. Movies repeated after months and years can be compared with each other and by various investigators. These movie records also constitute valuable teaching material.

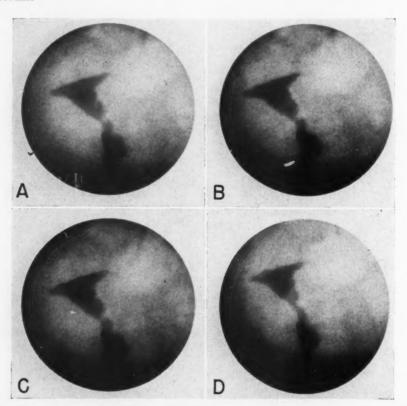


Fig. 3.—A 36-year-old patient. Sterility of 15 years' duration, positive Rubin test. Left lower quadrant pain for 2 weeks. A, B, C, D, Frames taken from cineradiograph demonstrating waves, visible especially at lateral parts of fundus. In the movie these frames appear on different levels, caused by swinging motion of the uterus.

- 4. The study of the physiology of the uterus and tubes is facilitated by cineradiography. By using the slow-motion technique, finer functional details are shown which cannot be visualized by either serial roentgenograms or fluoroscopy:
- A. Uterine filling, perceptible only faintly during simple fluoroscopy, can be observed distinctly by means of cineradiography combined with simultaneous fluoroscopic visualization, because of the intensified light.

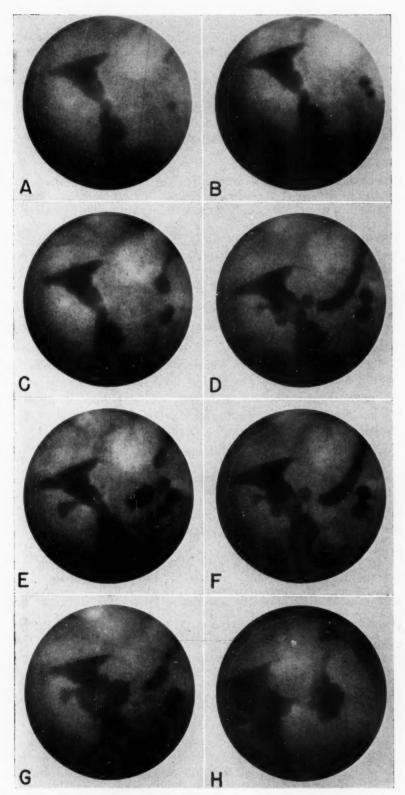


Fig. 4.—Same patient as in Fig. 3. Demonstration of tubal patency with Lipiodol. Contrast medium dropping into the cul-de-sac.

B. The movie seems to furnish evidence of a swinging motion of the uterus within its suspension apparatus, synchronized and simultaneous with the respiration.

C. Waves along the wall of the fundus are another kind of uterine motion observed during cineradiography. They are probably produced by the influx of the contrast material into the uterine cavity. Whether or not these waves are due to uterine contractions cannot be stated at present (Figs. 2, 3).

D. The tubes can be observed while being filled. If they are patent one actually sees the contrast fluid falling drop by drop from the fimbriated ends into the peritoneal cavity (Fig. 4).

5. Cineradiography which shows female organs in motion (or in slow motion) is an aid in the differential diagnosis of pathological conditions, while x-ray pictures are sometimes suggestive of nonexistent uterine pathology, such as endometriosis or polyps.

6. Cineradiography shows the complete sequence of uterine or tubal behavior, whereas only momentary phases can be seen by isolated or serial radiograms. Capturing the decisive moment is entirely subject to chance in the timing of a radiogram. It is the most important advantage of the new method to be independent of this chance factor.

Comment

This method is still very new. Consequently, our experience is as yet limited. Further advantages will come to light and more knowledge will become available as cineradiography will be used for the observation of a greater variety of pathological conditions of the female genital organs. Technical improvements, for instance a timing device and means of enlarging the area of visualization, are planned.

Summary

Cineradiography of female pelvic organs, a new type of hysterosalpingography, using 16 mm. movie film and continuous simultaneous visualization, is described and the advantages of the new method are discussed.

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CHLORPROMAZINE AND CHLORPROMAZINE COMBINATIONS IN THE TREATMENT OF DYSMENORRHEA

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BECAUSE of the many physiological and psychological factors that may influence menstruation, it is not surprising that there is no general agreement among investigators concerning the etiology of, or treatment for, painful menses. Numerous etiological theories have been advanced; many different treatments have been suggested.

Some of the newer drugs, particularly those with seemingly diversified pharmacodynamic actions, have been tried with questionable success.¹⁻⁵ The following report is concerned with an investigation of the effect of one of these new drugs, chlorpromazine,* in treating patients with primary dysmenorrhea. The first part of the study was designed to compare the effectiveness of chlorpromazine with that of APC (aspirin, phenacetin, and caffeine) and a placebo; the second part compares the effectiveness of a chlorpromazine-analgesic combination with that of an analgesic-narcotic combination.

Materials and Methods

The study was conducted on 48 student nurses who presented symptoms of dysmenorrhea. All underwent thorough pelvic and physical examinations to rule out possibilities of secondary dysmenorrhea. Generally, their case histories revealed that the patients were absent from their duties during menses and that bed rest and analgesic or sedative therapy offered little relief of pain. Six patients suffered from nausea and vomiting in addition to pain.

During the first part of the study a double-blind technique was used to dispense medications. Patients received six envelopes (one for each of six consecutive menstrual periods); two marked "A," two marked "B," and two marked "C." Envelope "A" contained APC capsules, envelope "B," placebo capsules, and envelope "C," 10 mg. chlorpromazine capsules. The capsules of each kind were to be taken once every four hours as needed for discomfort. All capsules looked identical and their contents were unknown to the investigator. A specially designed report form was attached to each envelope so that the patients could evaluate the efficacy of each medication as "good," "fair," or "poor." The study was designed so that during any one menstrual period one-third of the patients received APC, one-third placebos, and one-third chlorpromazine. Weights were taken before and after treatment in order to check the possible diuretic effect of the preparations.

^{*}Thorazine, Smith, Kline & French Laboratories, Philadelphia, Pa.

The second part of the study included two consecutive menstrual periods. During the first menstrual period, patients were told they were receiving a combination of 10 mg. chlorpromazine and Edrisal.* During their second period, patients assumed they were receiving chlorpromazine in some form, but were actually given a combination of ½ grain codeine sulfate and Edrisal. Patients were instructed to take each of the medications once every 4 hours as needed, and to evaluate the efficacy of these medications in the same manner as they had done previously.

Results

Eleven patients who failed to take the medication for 3 or 6 consecutive menstrual periods were dropped from the study. Twenty-eight patients took each medication for six menstrual periods; 9, for three menstrual periods. A total of 65 observations were obtained on each of the drugs. The results are shown in Table I. Twenty-eight observations were obtained for each of the combinations during the second part of the study. Results appear in Table II.

Table I. Efficacy of APC, Chlorpromazine, and Placebo in Treatment of Primary Dysmenorrhea

		NUMBER OF PATIENTS	
MEDICATION	GOOD RESULTS	FAIR RESULTS	POOR RESULTS
APC	. 27	10	28
Placebo	29	11	25
Chlorpromazine	27	19	19

Table II. Efficacy of Chlorpromazine-Edrisal and Codeine Sulfate-Edrisal in Treating Primary Dysmenorrhea

-	NUMBER OF PATIENTS			
MEDICATION	GOOD RESULTS	FAIR RESULTS	POOR RESULTS	
Chlorpromazine-Edrisal	24	3	1	
Codeine sulfate-Edrisal	25	3	0	

In addition to experiencing an amelioration of pain, the 6 patients who suffered from nausea and vomiting were relieved of their symptoms when they were taking chlorpromazine; the comparison of weights taken before and after chlorpromazine treatment did not show any diuretic effect of the drug. Except for a transitory drowsiness associated with chlorpromazine, no significant side effects resulted from any of the medications.

Comment

The results of this study demonstrate that the response to treatment for dysmenorrhea varies considerably from patient to patient. In 15 patients (usually, but not always, those with less severe symptoms) a placebo plus reassurance was all that was necessary; however, only 5 of the 15 responded consistently to the placebo. The number of patients who showed a placebo response was about that expected in a study of this type.

Each of the three preparations tested in the first part of the study proved equally effective in relieving pain. Chlorpromazine was particularly effective

^{*}Smith, Kline & French Laboratories brand name for Benzedrine sulfate (racemic amphetamine sulfate, SKF) 2.5 mg.; acetylsalicylic acid, $2\frac{1}{2}$ grains; phenacetin, $2\frac{1}{2}$ grains.

in patients whose dysmenorrhea was accompanied by a greater than usual amount of tension and anxiety, and in those suffering from nausea and vomiting.

The comparison of Edrisal plus codeine with Edrisal plus chlorpromazine showed that both combinations were highly effective. Edrisal has proved to be a good treatment for dysmenorrhea in many instances. It was expected that the addition of a narcotic would increase the analgesic effect of Edrisal considerably. It was not as certain that chlorpromazine, by altering the patient's attitude toward pain, would prove of equal value. The fact that it did indicates that substituting chlorpromazine for codeine or other habit-forming narcotics may lessen the chances of creating drug addiction without appreciably detracting from the analgesic effect.

Summary

In order to test the efficacy of chlorpromazine in treating dysmenorrhea, the drug was compared with APC and a placebo in a double-blind study involving 48 patients. Eleven patients who failed to take the medications for three consecutive menstrual periods were dropped from the study. Twentyeight patients received the medications during six menstrual periods; 9 during three periods. A total of 65 observations were obtained on each of the three medications.

The 28 patients who received the first three medications for six periods were then used to evaluate two combinations of drugs: Edrisal (amphetamine, aspirin, and phenacetin) plus codeine, and Edrisal plus chlorpromazine. Twenty-eight observations were made on each combination.

Each of the three medications tested in the first trial proved equally effective in relieving pain. Chlorpromazine was particularly effective in relieving tension, nausea, and vomiting.

The second part of the study demonstrated that chlorpromazine plus Edrisal was as effective in relieving pain as was codeine plus Edrisal. Both combinations were highly effective.

It is concluded that chlorpromazine is a valuable addition to the available treatments for dysmenorrhea, particularly when this condition is severe enough to cause vomiting or to require narcotics in its treatment.

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Case Reports, New Instruments and Methods

TUBOPLASTY: FREE-WHEELING THE POLYETHYLENE SPLINT

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SURGICAL correction of obstructive sterility in women has been greatly implemented by the employment of biologically inert polyethylene tubing as a splint for recanalization of Fallopian tubes, and a mold over which endosalpinx may re-establish its hollow continuity from ovary to endometrium.

One of the drawbacks to this advancement has been the need for suture fixation of the plastic tubing to the natural canal in a fashion still permitting harmless, if not painless, removal.

The following proposals represent modifications in the basic scheme of threading lengths of polyethylene tubing through (reopened) Fallopian tubes and uterine cavity, fixing the plastic material in place with sutures to the fimbriated ends of the tubes, cervix, and/or the abdominal wall, then allowing the ends to "dangle" into the vagina, into the peritoneal cavity, or from the abdominal wall. Subsequent removal requires cutting fixation sutures at the cervix, ampullae, or abdominal wall, with or without laparotomy, and "jerking" the plastic prosthesis free from other stitches along the genital canal.

Technique

When only a single length of polyethylene tubing is employed, passed through both Fallopian tubes, forming a loop in either the endometrial or the peritoneal cavity, and the ends are allowed to dangle through the abdominal wall or into the vagina, no sutures are required between the synthetic and natural tubes to maintain the two in their proper relationships. Further, there now remain no "stump ends" of plastic material projecting into the peritoneal cavity to irritate the lining membrane. The method employing a loop within the endometrial cavity (Fig. 1 and Figs. 2A and 2B) and bringing the ends out through the abdominal wall poses no more hazard of internal hernias than methods using separate lengths of tubing, fixed to salpinx, and exteriorized.

In the second modification (Fig. 3), leaving a loop of polyethylene tubing in the peritoneal cavity conjures up visions of intestines obstructed by intertwining with the synthetic "band." It is comforting to know that, under such circumstances, the offending mechanism, the loop, may at any chosen moment be withdrawn, or "jerked" free with no fear of avulsing any fixation sutures en route.

Practically speaking, these two modifications eliminate all the operating time usually consumed in suturing the plastic splint into place, and also the special instruments and personnel previously required for "fishing" the prosthesis from the uterine cavity through the cervix, with or without the benefit of a third, or midfundus "window" incision, while the abdomen is open.

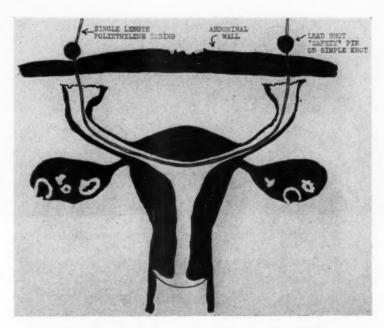


Fig. 1.—Shows polyethylene tubing with loop in uterine cavity.

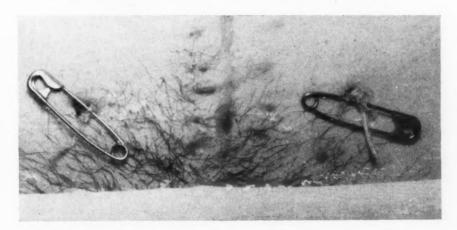


Fig. 2A.—Shows knots in ends of tubing and additional safety pins, 4 weeks postoperatively.

To form the loop in the endometrial cavity, one end of the polyethylene tubing is first inserted into the butt of a small-caliber soft-rubber catheter. This "shuttle" is then introduced into the uterine cavity through a stab wound in the cornu. Through a like wound in

the opposite cornu, a fine hemostatic forceps is introduced, and the catheter is caught in its jaws and withdrawn, delivering the tubing preparatory to threading it through the Fallopian tube of that side.

If the peritoneal loop method is chosen, two catheters are used, each holding an end of polyethylene tubing in its lumen, having already been threaded through the Fallopian tubes.

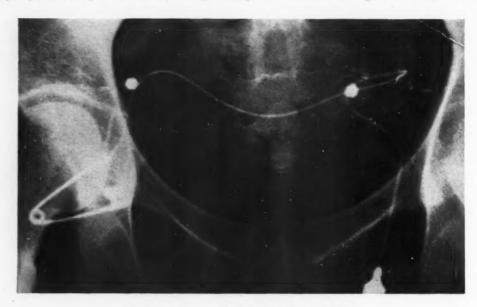


Fig. 2B.—Shows tubing filled with Lipiodol.

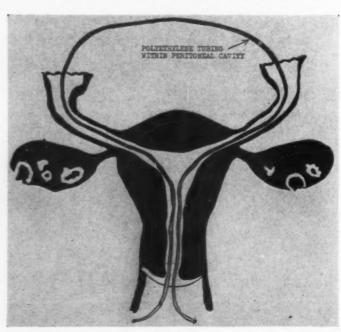


Fig. 3.—Illustrates tubing with loop in abdominal cavity and ends protruding into vagina.

The catheters are passed through cornual wounds on the appropriate side, into the uterine cavity, on through the cervix, where they must be caught by a nonsterile member of the operating room personnel, and withdrawn, to take up excess slack in the loop.

The proposed modifications are expected to expedite the modus operandi, if not improve the statistical results, since they do not alter the principles of the basic procedure.

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FIXATIVE AND STAINING CYTOLOGIC TECHNIQUES

Proposed Modification of the Papanicolaou Methods

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THE purpose of this communication is to present a modified Papanicolaou staining procedure. It has been used in our laboratory for the past four years and found to be satisfactory for smears prepared for cytologic study from the skin, oral cavity, breast, pharynx, larynx, trachea, bronchi, esophagus, stomach, urinary bladder, cervix uteri, corpus uteri, rectum, and sigmoid colon.

The difficulties and inconveniences of obtaining and storing absolute alcohol, its great cost, and the multiplicity of steps involved made a simplified technique desirable.

In the early stages of the introduction of the cytologic technique and its limitation to the cervix and corpus uteri, the problem of a complicated staining technique was relatively unimportant. Since the method has been extended to so many epithelial surfaces of the body, however, as a result of the introduction of new instruments and methods for obtaining cytologic material, a complicated staining technique becomes a handicap.

Comparative Studies

To ascertain the comparative value of the proposed modified method, careful studies were carried out using various materials and methods. The stains used in all the procedures were those introduced by Papanicolaou.

Five cervical cytology smears were taken from each of 15 patients and placed on each of five slides using the Ayre wooden spatula, as much care as possible being taken to see that the same amount of material from each patient was placed on each slide. The slides were fixed at once in a freshly prepared solution consisting of equal parts of ether and 95 per cent ethyl alcohol. They were stained with the use of five different procedures and the findings were compared.

In another series of cases the same number of smears were similarly prepared and processed with the exception that pure methyl alcohol was used as a fixative instead of ether and alcohol. For the purpose of this study the staining procedures will be classified as:

- A. S29 dehydrant procedure.
- B. Classic Papanicolaou.1
- C. Modified Papanicolaou.*
- D. Isopropyl alcohol procedure.
- E. Methyl alcohol procedure.

^{*}This modification has been introduced by the Ortho Pharmaceutical Co., Raritan, N. J., and described in detail in one of their circulars. It varies from the classic Papanicolaou method in using methanol in place of ethanol (see Tables I and II).

TABLE I. STAINING PROCEDURES

	A	В	C	D	E
1.	Rinse aq. dist.	Rinse 70% ethanol	Rinse 95% methanol	Same as	Same as
2.	Stain hem. 4-6 min.	Rinse 50% ethanol	Rinse 70% methanol	В	В
3.	Rinse .05% HC1	Rinse aq. dist.	Rinse aq. dist.	using	using
4.	Rinse tap H ₂ O	Stain hem. 5-10 min.	Stain hem. 4 min.	isopropyl	methano
5.	Rinse lithium carb.	Rinse aq. dist.	Rinse aq. dist.	alcohol	instead
6.	Rinse tap H ₂ O	Rinse 0.5% HC1 6	Rinse 70% methanol	instead	of
7.	Rinse S29 dehy-	times	Rinse 70% methanol		ethanol
	drant*	Rinse in H ₂ O	+ 1% HC1	ethanol	
		Rinse lithium carb.			
8.	Rinse S29 dehy-	Rinse in H ₂ O	Rinse 70% methanol		
	drant	Rinse aq. dist.			
9.	Stain OG6 1 min.†	Rinse 50% ethanol	Rinse 70% methanol		
10.	Rinse S29 dehydrant	,,	Rinse 70% methanol		
	•	Rinse 70% ethanol	+ 3% NH ₄ OH		
11.	Rinse S29 dehydrant	Rinse 80% ethanol	Rinse 70% methanol		
12.	Stain EA50 3-5 min.;	Rinse 95% ethanol	Rinse 70% methanol		
13.	Rinse S29 dehydrant	Stain OG6 1 min.	Rinse 70% methanol		
14.	Rinse S29 dehydrant	Rinse 95% ethanol	Rinse 95% methanol		
15.	Clear xylol	Rinse 95% ethanol	Stain OG6 1½ min.		
16.	Clear xylol	Stain EA36 2 min.	Rinse 95% methanol		
17.	Mount	Rinse 95% ethanol	Rinse 95% methanol		
18.		Rinse 95% ethanol	Stain EA50 2 min.		
19.		Rinse 95% ethanol	Rinse 95% methanol		
20.		Rinse in absolute	Rinse 95% methanol		
21.		ethanol	Rinse 100% ethanol		
		Rinse in absolute	Clear xylol		
22.		ethanol and xylol			
		Clear in xylol	Mount		
23.		Mount			
24.					
Results	Good	Good	Poor	Good	Poor

*Diethylene glycol monoethyl ether acetate-isopropanol (prepared and manufactured by the Technicon Chemical Company, Chauncey, N. Y.).

†Single orange G stain. Orange G and phosphotungstic acid prepared and manufactured by the Ortho Pharmaceutical Corporation, Raritan, N. J.

‡Multiple polychrome stain. Light green S. F. yellowish, Bismark brown Y., eosine Y., phosphotungstic acid, glacial acetic acid prepared and manufactured by the Ortho Pharmaceutical Corporation, Raritan, N. J.

TABLE II. RESULTS WITH TWO FIXATIVES

	PROCEDURE				
	A'	В	C	D	E
Ether and alcohol fixative	Good	Good	Poor	Good	Poor
Methanol fixative	Good	Good	Poor	Good	Poor

Results and Comments

With the use of the five different staining procedures as outlined, the results, as was expected, varied from case to case but in individual cases there was a similarity in three of the five methods (Table I). The exceptions were the modified Papanicolaou (methyl alcohol) (C), and the methyl alcohol (E) methods, where most of the cellular elements took on a very pale stain which made interpretation in this laboratory more difficult.

The results obtained by the five methods of staining using smears fixed in methyl alcohol compared very closely to the results obtained when etheralcohol fixative was used (Table II). With the classic Papanicolaou (B), S29 (A), and isopropyl alcohol (D) staining procedures, the results were indistinguishable from the results obtained with the same methods when the smears were fixed in ether-alcohol solution. The two methyl alcohol staining procedures exhibited the same pale-staining reaction as that obtained with the use of the ether-alcohol fixative.

Am. J. Obst. & Gynec. August, 1957

While there are many methods of staining cytologic material, the individual worker obtains the best results with the method with which he is most familiar. A simpler but equally efficient staining procedure, utilizing less costly and more easily attainable materials, should have wide use.

The time required for the "stains" depends on the age of the stain, or the length of time it has been in actual use. At the beginning of the week when the stains are fresh, the shorter staining time tested above is required. Staining time is at a minimum when fresh stains are used daily.

It must be recognized, however, that a perfect stain of every slide in every batch is unattainable regardless of the staining method used, since factors extrinsic to the stain may be involved, e.g., presence of excess mucus, white blood cells, red blood cells, bacteria (not including *Bacillus vaginalis* and free nuclei) or other foreign material which might retard or impair the action of the stains on the cells.

The use of methyl alcohol for the preservation of blood and marrow smears, where perfect preservation of the cellular detail is of paramount importance, indicates that this is an excellent fixative. Its use would seem obvious in cancer cytology where the preservation of cellular detail is of equal importance. The high volatility, too, of ether makes the preservation of the original 1:1 ratio of ether-alcohol fixative difficult. Solutions prepared ahead of time tend to lose some of their ether content, impairing the fixative properties of ether-alcohol. In contrast, methyl alcohol, not being a mixture, will be unaffected by evaporation. This fact is of importance to the centers that receive smears in fixative solutions. In addition, it is more convenient for the practicing physician to use pure methyl alcohol as a fixative solution instead of preparing fresh solutions of ether and alcohol.

It is well known that the use of S29 dehydrant does not cause cellular distortion in staining sections of histologic material. This study shows that its use does not cause distortion in cytologic material.

Conclusions

In a series of cytologic smears stained according to various procedures, with two different fixative solutions, comparable results were obtained by the classic Papanicolaou (B), the S29 dehydrant (A), and isopropyl (D) techniques. The S29 dehydrant procedure involves fewer steps, does not require diluting, can be changed quickly, and is more economical than absolute alcohols. In addition, its feasibility in automation is apparent. The procedure has been adapted for use with the Autotechnicon. Details will be published elsewhere.

Summary

- 1. The S29 dehydrant procedure in the staining of various types of smears for cytologic study has been found to give excellent results.
- 2. The use of pure methyl alcohol as a fixative for various types of smears for cytologic study gives excellent results comparable in every way with freshly prepared ether-alcohol solution.
- 3. The availability and low cost of S29 dehydrant and pure methyl alcohol are factors of great importance.
- 4. The many advantages pertaining to the use of S29 dehydrant staining procedure and the use of methyl alcohol as a fixative are discussed.

Acknowledgment is given to Mrs. Sigrid Taranuk, Cyto-Technician, of The Cytology Institute for Cancer Detection, for her efficient help in this study.

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DEATH FROM AIR EMBOLUS. REPORT OF A CASE FOLLOWING TUBAL INSUFFLATION

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E VEN a cursory review of the literature discloses many unusual and bizarre causes of death from air embolus. Goddard and Moffett¹ described the following types of cases reported: (1) vaginal insufflation and douches during pregnancy; (2) cesarean section; (3) antral irrigation; (4) attempted self-abortion; (5) tubal insufflation; (6) urethroscopy with air inflating urethroscope; (7) intentional introduction of air into cavities or potential cavities—pleural, peritoneal, retroperitoncal or perirenal spaces, bladder, joint cavities, paranasal sinuses, and eustachian tube; (8) operations on breast, thyroid, lungs, and prostate; (9) blood donation; (10) blood transfusion; (11) high-altitude flying; (12) deep-sea diving.

In addition to these, Scrimgeour and Carrick² reported the occurrence of this mishap in 2 cases of ruptured uteri, and McCullough and Morales³ reported a case following postpartum surgical sterilization. This apparently was caused as a result of uterine traction while the patient was in Trendelenburg position, presumably drawing air into the vagina, the air subsequently being forced into the uterus and its sinuses as a result of resumption of the supine position, and prevention of egress of air from the vagina because the patient's thighs were being held tightly together.

Air embolus from insufflation therapy for Trichomonas is a not unusual occurrence, numerous cases having been reported, among them those of Peirce,⁴ Brown,⁵ Partridge,⁶ Cooke,⁷ and Breyfogle.⁸ Embolus following tubal insufflation has been a not-unexpected complication of this investigative procedure and the reports by Faulkner,⁹ Finn,¹⁰ Moench,¹¹ and others and the admonitions of Rubin¹² have resulted in the substitution of carbon dioxide as a preferable gas instead of air for this procedure.

Numerous comparisons, however, have been made concerning the relative dangers of carbon dioxide and air as embolus producers, and Nitsche¹³ reported 2 cases of attempted suicide, in one of which 60 c.c. of air was injected into an antecubital vein without death, and in another 20 c.c. on two different occasions, without adversely affecting the individual with suicidal intent. Moore and Braselton¹⁴ confirmed the finding that apparently a very large amount of air has to enter a peripheral vein before death occurs, and made a comparison of the amounts of oxygen and air necessary to produce death in animals, the minimum fatal dose of oxygen being 10 per cent greater than

the minimum fatal dose of air. In comparing the relative dangers of carbon dioxide and air when injected into the pulmonary vein in cats, these authors found that 0.25 c.c. of air per pound of body weight was ineffectual in producing any change. This would represent the same amount as 37.5 c.c. in a 150 pound man, whereas over 0.5 c.c. per pound was always fatal. However, with carbon dioxide, up to 3 c.c. per pound (or 450 c.c. in a 150 pound man) had no effect. These authors pointed out, however, that these were all experiments in injecting gas into the *pulmonary* vein, which was considerably different from injection into a systemic vein. They also made the interesting observation that every sample taken from commercial carbon dioxide tanks had appreciable amounts of air in it.

Harkins and Harmon,¹⁵ injecting air and oxygen into the peripheral circulation of dogs, found the minimal fatal dose of air to be 8 c.c. per kilogram, and of oxygen the same.

The following case is presented as a graphic and tragic example of the use of any gas for purposes of insuffiction during plastic operations on the Fallopian tube, a relatively common practice among gynecologists who do this kind of operative procedure.

M. F., aged 21 years, was admitted to the Gynecology Service of the Grace-New Haven Hospital on Dec. 6, 1955, for a tubal plastic operation. At the age of 13 she had had a bilateral salpingectomy in another hospital, apparently because of bilateral salpingitis. Six months after her marriage, the patient and her husband requested an attempt at plastic reconstruction of the tubal stumps, even though they were made fully aware of the meager possibilities of its successful outcome. The husband's sperm count was normal, the postcoital test at the ovulation date showed many viable sperm, and the patient's premenstrual endometrial biopsy disclosed normal secretory endometrium. A salpingogram showed bilateral tubal lumina, extending through what was thought to be the intramural portion of the tube and possibly for a centimeter beyond this. A tubal plastic operation was then arranged for Dec. 7, 1955.

Six days after the patient's last menstrual period, with Pentothal and ether anesthesia, she was placed in lithotomy position and a cannula inserted through the cervix and held in place by attachment with a tenaculum which grasped the anterior cervical lip. The cannula was attached to a Jarcho insufflation apparatus, and trial insufflation carried out, which confirmed closure of the tubes. With the cannula in place, the patient was then placed in modified Trendelenburg position, prepared, and draped. The old abdominal suprapubic incision was excised, and when the peritoneal cavity was opened, numerous adhesions were found between the omentum, the intestines, and the pelvic structures. These were divided by blunt and sharp dissection and it was disclosed that the left ovary had apparently been removed at the time of the previous bilateral salpingectomy, but the right ovary appeared fairly normal, although it had on it some residual, ragged adhesions. The stumps of both tubes were about 1 cm. in length and were densely adherent to the cornual areas of the uterus. These adhesions were carefully divided and the distal portion of the left tube was incised. Insufflation with the Jarcho apparatus at this time produced bubbles of air which came through the cut portion of the tube, the pressure of air in the Jareho apparatus being 50 or 60 mm. of mercury. A similar procedure was carried out on the right side and tubal patency established in a similar fashion.

A decision was made to insert a probe through both tubal lumina in a fashion which would make it possible to thread a polyethylene catheter through both the tubal stumps into the uterine cavity during which procedure the cervical cannula was to be removed by

an assistant, and the probes which had been threaded into the uterine cavity passed through the cervix and also grasped by the assistant with the expectation of, later, suturing the polyethylene catheters to the cervix so that they would remain firmly in place. It was planned to attach a disc of polyethylene sheeting to the tubal end of the polyethylene tubing in a mushroom-shaped fashion, and suture it to the serosal surface of the cornua so as to prevent adhesions from forming again around the artificially opened tubal stumps. These polyethylene structures were to be removed at a subsequent operation.

Considerable probing was necessary before the polyethylene-threaded probe could be inserted into the uterine cavity, and inevitable trauma to the endometrial surface must have resulted from this manipulation. Finally, however, a probe was satisfactorily placed through one tube and a similar procedure was being carried out on the other tube when the patient's heart suddenly stopped beating. Attention is called to the fact that during this repeated probing in the attempt to insert the polyethylene catheters, the patency of the tubes was frequently tested by insufflation with the Jarcho apparatus.

Following the cardiac arrest the patient's chest was immediately opened and by cardiac massage resumption of the heartbeat was established within a minute and a half. The patient's head and upper thorax remained deeply cyanosed, however, and the heart did not beat in a satisfactory fashion. Ventricular fibrillation occurred which was immediately controlled by an electrical defibrillator. Calcium gluconate was injected into the left ventricle, and it was noticed that upon slight withdrawal of the plunger of the syringe, air was found to be present in the left ventricular cavity. Ten or 15 c.c. of air was expressed from the left heart and possibly as much more from the right. The patient's heart then developed a more normal rhythm. Artificial respiration was continued, Levophed* was administered to the patient to maintain her blood pressure, and her thoracic and abdominal incisions were closed. She was placed in a respirator but died after 18 hours of artificial respiration, artificial maintenance of the blood pressure with Levophed and epinephrine, and no return of consciousness. It was estimated that she had been cerebrally anoxic for at least 15 minutes even though resumption of the heartbeat had been established within a minute and a half, and a conclusion was made that she must inevitably have had extensive cerebral damage as a result of the anoxia. Permission for autopsy was not obtained.

In retrospect, a reconstruction of the events of this case led to the conclusion that the amount of gas which was found in the circulation would have produced death even if it had been carbon dioxide, and that the trauma to the uterine wall by the probe during the attempts to insert the polyethylene catheter in all probability opened sufficient venous sinuses so that the repeated insufflation to demonstrate tubal patency introduced air directly into the circulation.

Although I have not used air for routine office insufflation for many years, the practice of continuing the use of air insufflation during tubal plastic operations was thought to be relatively innocuous. As a rule, a minimal amount of air only is used during the operation to demonstrate tubal patency. The repeated insufflation of air or any other gas as carried out during the above-outlined procedure is certainly ill advised. Tubal plastic operations have since been carried out with the assistance of an insufflation apparatus containing saline solution tinged with methylene blue. This has proved to be highly satisfactory.

^{*}Levarterenol bitartrate, Winthrop Laboratories, New York, N. Y.

Summary

A brief and partial review of the literature concerning air embolus and a comparison of the amounts of air, carbon dioxide, and oxygen which produce emboli is presented.

A case of fatal air embolus during a tubal plastic operation is reported. What were thought to be the probable causes of the air embolus are discussed and appropriate changes in technique described.

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ENDAMOEBA HISTOLYTICA IN LEUKORRHEA AND SALPINGITIS

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A MEBIC dysentery is a very common disease in India, so that research on the *Endamoeba histolytica* as a possible cause of leukorrhea seemed important.

In a series of 123 patients, a sample of the discharge was taken from the posterior fornix by means of a thin glass tube. The discharge with a little normal saline added was placed on four slides, covered by a cover slip, and microscopic examination carried out. The results are shown in Table I.

When *Endamoeba histolytica* was found in the vaginal discharge, the stool was also examined and invariably found positive for *Endamoeba histolytica*. These patients all were also found to have a past history of dysentery.

In another series of 26 cases, examination was made of Fallopian tubes removed at operation for salpingitis. The tube was pressed between two slides, a few drops of saline added to the smeared material, and microscopic examination again made (Table II).

The patients in whose tubes *Endamoeba histolytica* was thus found were also shown to have the organism in their stools and to have a past history of dysentery.

TABLE I. RESULTS OF MICROSCOPIC EXAMINATION OF DISCHARGE IN 123 CASES OF LEUKORRHEA

AGE GROUP	NO. OF CASES	ENDAMOEBA HISTOLYTICA	MONILIA	TRICHOMONAS VAGINALIS
11-20 yrs.	24	3	2	4
21-30 yrs.	29	5 .	6	7
31-40 yrs.	38	4	5	8
41-50 yrs.	32	2	4	6
Total	123	14	17	25

TABLE II. RESULTS OF EXAMINATION OF FALLOPIAN TUBES FOR ENDAMOEBA HISTOLYTICA

AGE GROUP	NO. OF CASES EXAMINED	NO. OF CASES POSITIVE FOR ENDAMOEBA	HISTOLYTICA
16-25 yrs.	6	0	
26-35 yrs.	12	1 (Multipara, aged 28)	
36-45 yrs.	8	1 (Multipara, aged 36)	
Total	26	2	1

Conclusion

In addition to the well-known sites of damage by the *Endamoeba histolytica*, namely, the intestinal tract, liver, gall bladder, and lungs, the organism may be the cause of lesions in the female reproductive tract, notably the Fallopian tubes and vagina.

ENDOMETRIAL CARCINOMA IN A 25-YEAR-OLD WOMAN DISCOVERED ON ROUTINE STERILITY INVESTIGATION

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IN 1951 Dockerty, Lovelady, and Foust reported 36 cases of adenocarcinoma of the endometrium occurring in women under 40 years of age. This group comprised 2.1 per cent of the total number of carcinomas of the endometrium (1,694) seen at the Mayo Clinic over a forty-year period. They emphasized that in this age group there was a high incidence of hypertension, obesity, diabetes, and sterility. It is because of this latter factor that this case report is presented.

Case Report

Mrs. H. H., a 25-year-old Negro woman, gravida 0, was first seen in the Jefferson Davis Hospital Gynecological Clinic on Dec. 16, 1954. Her reason for reporting to the clinic was infertility. A preliminary general physical examination and a pelvic examination were completed with essentially normal findings, and the patient was then referred to the sterility clinic. Sterility work was begun on Jan. 12, 1955. Examination of the husband's semen showed a sperm count of 68 million per cubic centimeter with 90 per cent motility and 90 per cent normal forms. A complete blood count was done which showed moderate anemia, the hemoglobin being 9.9 Gm. with hematocrit of 34 per cent. The white blood cell count was 16,400 with a normal differential. Chest and skull films were reported as normal. A Rubin test was performed on Feb. 16, 1955. There was no evidence of tubal patency.

An endometrial biopsy taken on the first day of her next menstrual period was reported as "endometrial tissue, proliferative pattern, with minimal mitotic activity." One week after the completion of this menstrual period, a hysterosalpingogram was done with the use of Skiodan and acacia. The report of this hysterosalpingogram was as follows: "The uterine cavity is normal in size but is irregular in contour and there are some filling defects in the uterine cavity which might be blood clots. The right tube is well demonstrated and is patent. There is a small amount of dye in the left tube." On the first day of the following menstrual period a repeat biopsy was taken and the report obtained was: "Endometrial tissue, adenocarcinoma." As soon as this report was received the patient was hospitalized and dilatation, curettage, and multiple cervical biopsy were performed. Examination under anesthesia showed an essentially normal pelvis and the uterus did not appear to be enlarged. The pathology report of the curettage and biopsy was: "Endometrial tissue, hyperplasia of endometrium, squamous metaplasia and adenocarcinoma. Cervicitis, chronic, with epidermalization." Treatment consisted of intracavity and intravaginal radium, followed in eight weeks by total hysterectomy, bilateral salpingo-oophorectomy, and partial removal of the upper part of the vagina. The patient tolerated her surgery very well. The postoperative course was uneventful and she was dismissed on the sixth postoperative day.

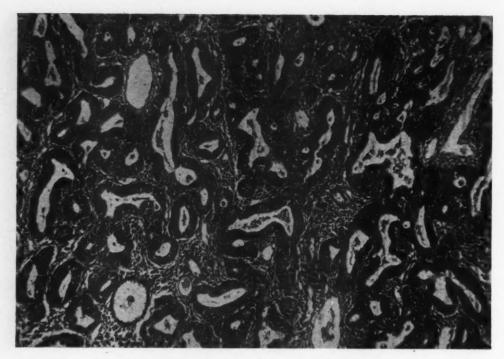


Fig. 1.—Endometrial biopsy which shows adenocarcinoma.

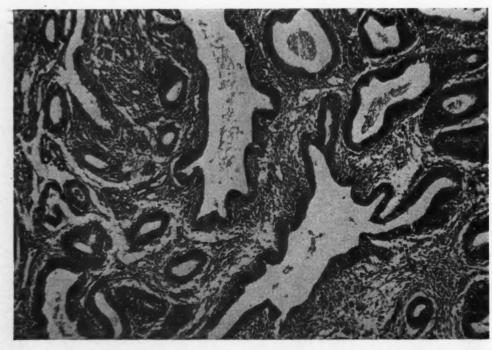


Fig. 2.—Curettement. This shows graduation from atypical endometrium to frank adenocarcinoma.

The pathological report on the removed material was as follows: "Cervix uteri: cervicitis, chronic; endometrium, atrophy and fibrosis; uterus, no significant change; fallopian tubes, salpingitis, chronic; ovaries, fibrosis; appendix, no significant change. Comment: The previously described changes are probably a result of radiation therapy. No evidence of residual carcinoma seen either grossly or microscopically."

This patient at the present time is being followed in the cancer clinic and has no evidence of any recurrent disease in the pelvis.

Summary

A case of endometrial carcinoma in a patient 25 years of age was picked up on routine sterility investigation by endometrial biopsy. It is of interest to note that in a study of 36 cases of adenocarcinoma of the endometrium occurring in women under the age of 40 Dockerty, Lovelady, and Foust stressed that infertility was a prominent clinical feature in these patients.

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A MODIFIED VAGINAL SPECULUM AND TISSUE COLLECTOR

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THE Auvard and Garrigue weighted specula have been standard equipment for exposure of the cervix during vaginal procedures and uterine curettages. The reasons for modifying these specula are: (a) the difficulty of sending to the pathologist curettings which are sufficient for processing and diagnosis and, (b) the occasional failure of these instruments to remain in place.

The most common methods used today for the collection of curetted material involve the use of gauze or bent spoons under the cervix, or the placing of a cup beneath the weighted portion of the speculum. The instrument here described was designed in an effort to combine a more efficient speculum with a tissue collector.

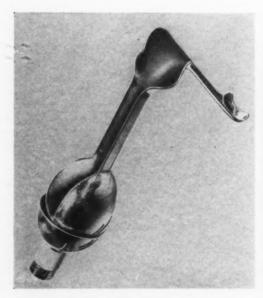




Fig. 1.

Fig. 2.

Fig. 1.—The speculum with the tissue-collecting cup in place. Fig. 2.—The speculum with cup detached.

Fig. 2.—The speculum with cup detached.

The instrument* consists of two parts: the speculum and a detachable cup which is designed to hold either scant or abundant amounts of tissue. The accumulated blood escapes from the many holes around the base of the cup.

^{*}This instrument is manufactured by J. Sklar and Company, 38-04 Woodside Ave., Long Island City, New York.

The speculum itself consists of a single instrument that weighs 3 pounds, with a concave vaginal blade 1 cm. longer than usual, with a vertical elevation of 11 mm. at its distal end. The latter is designed to prevent tissue from entering the vagina and, at the same time, to elevate the cervix slightly. The concave vaginal blade acts as a trough for the tissue and the increased length helps to prevent the speculum from slipping out of the vagina.

Grateful acknowledgment is accorded to the following: Dr. Edward Solomons, Director of Obstetrics and Gynecology at Maimonides Hospital of Brooklyn and Professor of Obstetrics and Gynecology at the State University of New York College of Medicine; members of the Attending Staff at Maimonides Hospital of Brooklyn; Messrs. R. G. Bates and D. Zalkind of J. Sklar and Co., for their cooperation in the development and construction of this instrument.

MONOAMNIOTIC TWIN PREGNANCY

With Report of Three Cases of Double Survival, One of Them With Knotted Cords

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(From the Jewish Hospital of Brooklyn)

THE anatomy of the placenta and membranes, in cases of identical twins, depends on the embryological time of division or twinning of the developing single fertilized ovum.² About one third of single ovum twins are dichorionic and diamniotic, arising from the first two totipotential blastomeres, and such twins cannot be differentiated from fraternal twins by a study of the anatomy of the placenta and membranes. About two thirds of single ovum twins are monochorionic and diamniotic; these arise in the blastocyst stage by the division of the inner mass or, more likely, by the formation of two separate inner cell masses. Rarely, when the embryonic plate divides after the primitive amnion has formed, two embryos will develop within a single amniotic sae, giving rise to monochorionic, monoamniotic twins.

At a somewhat later stage, when the embryonic disk is partly organized, attempts at division will be incomplete and conjoined monsters will result. Such monsters are always within a single amniotic sac and those that have survived (Siamese twins) have always exhibited opposite handedness. According to Guttmacher, 48 per cent of identical twin pairs exhibit opposite handedness. We must, therefore, assume that the differentiation of sidedness must occur during the blastocyst stage; therefore, all sets of monoamniotic twins should be of opposite handedness.

It is of little, practical value to attempt to compute the incidence of monoamniotic twins because many cases are undoubtedly missed by those not alerted to the condition. Following the recognition of the first of our cases, all of the twin placentas were carefully examined at the Jewish Hospital of Brooklyn for a period of about two years and during the course of about nine thousand deliveries. This included about 130 twin deliveries. Most of the twin placentas were examined personally by one of us. Only two other cases of monoamniotic twin pregnancy were discovered. We may conclude that the incidence, though small, is probably higher than generally calculated.

In 1935, Quigley⁸ collected 109 cases from the world literature. He reported a 68 per cent fetal mortality rate due to the twisting of the cords. He did not discover any instances of double survival, but he reported the first instance of the survival of one of the twins in the American literature.

The cases of monoamniotic twins with double survival thus far reported in the American literature are summarized in Table I.

TABLE I.

AUTHORS	DATE	NO. OF CASES	PRESENCE OF KNOTTED CORDS
Parks and Epstein ⁷	1940	1	Yes
Coulton, Hertig, and Longs	1947	2	No, neither case
King et al.6	1952	2	Yes, both
Haywood and Stokes ⁵	1953	1	Yes
Charlton, Winston, and Chomko1	1953	2	Yes, both
Present Authors	1955	3	Yes, in one case only

As noted by practically all of the authors on the subject, the chief problem in monoamniotic twin pregnancy is the knotting of the umbilical cords at some time before birth. This can result in the antenatal death of one or both of the twins due to obstruction of the fetal circulation. Furthermore, at delivery, when both twins are alive and the cords are knotted, the second twin may be lost following the prolapse of the knotted cords after the delivery of the first twin. The life of the second twin may often be saved by rapid delivery.

The diagnosis of monoamniotic twin pregnancy cannot be made prior to delivery. The diagnosis is usually made by the obstetrician when a second bag of waters is absent or when a mass of knotted cords prolapses after the delivery of the first twin. When the cords are not knotted and the obstetrician is not astute, the diagnosis may not be made until the placenta is examined by the pathologist. The condition should always be suspected when one or both of the twins are stillborn.

The cases to be presented here are the ninth, tenth, and eleventh of double survival recorded in the American literature and the seventh case of double survival in spite of the presence of knotted cords.

Case Reports

Case 1.—Mrs. E. P., a 24-year-old white woman, had a spontaneous term delivery of a 6 pound, 8 ounce child in 1951, and later the same year she had a spontaneous abortion at 10 weeks. With her twin pregnancy she had a normal antepartum course until she went into labor at 37 weeks' gestation on July 21, 1953. After a first stage of 1 hour and a second stage of 1 hour and 37 minutes the first child was delivered by a midforceps rotation operation. At this time a tangled mass of knotted cords presented. The second child was delivered five minutes later by internal podalic version and breech extraction under cyclopropane anesthesia. The male twins weighed 4 pounds, 7 ounces and 5 pounds, 0 ounces, respectively, and both survived. The placenta was photographed as shown in Fig. 1, although the photographer did us the unkindness of untangling the knot.

Case 2.—Mrs. R. H. This was the first pregnancy of a 16-year-old Negro girl. The mother had an uneventful antepartum course except for a mild anemia (hemoglobin 9.5 grams per cent) which was treated with hematinics. She went into labor at 39 weeks' gestation on Aug. 21, 1954. After a 10 hour first stage and a 55 minute second stage, the first child was delivered spontaneously as a vertex. An amniotic sac was not found and the second cord did not prolapse. Almost immediately the feet of the second twin presented and it was easily delivered by breech extraction two minutes after the delivery of the first twin. The male infants weighed 5 pounds, 5 ounces and 5 pounds, 10 ounces, respectively, and both survived. The placenta is not illustrated because it appeared very similar to that in case 1.



Fig. 1.—Placenta of Case 1. Unfortunately the cords were disentangled prior to photography. It may be noted that there is no dividing membrane between the roots of the umbilical cords. Also, the vessels course freely from one side of the placenta to the other. The insertions of the umbilical cords onto the surface of the placenta are in close proximity.

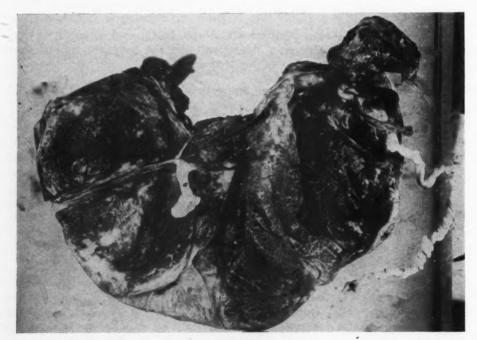


Fig. 2.—Placenta of Case 3.* Cesarean section for central placenta previa. The placenta filled the lower uterine segment and was, therefore, shaped like half of a spherical shell. It was partly torn when manually removed at section. The two infants were contained within a single sac and no remnant of a partition membrane could be identified.

^{*}Permission was granted for the inclusion of this case by Dr. Ralph Schwartz of the Jewish Hospital of Brooklyn.

CASE 3.-Mrs. J. K. was a 25-year-old white woman who had had a previous full-term delivery in 1952. In the seventh month of her second pregnancy an x-ray diagnosis of twins was made. At 33 weeks' gestation the patient was hospitalized for four days because of an episode of rather profuse painless vaginal bleeding, but no transfusion was necessary. A lesser bleeding episode occured at 35 weeks. At 37 weeks, she began to have mild irregular uterine contractions and slight vaginal staining. Vaginal examination in the hospital at 38 weeks disclosed a firm cervix, 3 cm. dilated, with a central placenta previa. The female babies were immediately delivered by cesarean section on Aug. 25, 1955. They weighed 5 pounds, 71/2 ounces and 4 pounds, 71/2 ounces, respectively. The placenta covered the entire internal os. A single amniotic sac contained the two fetuses, but no knotting of the cords was noted. Both babies survived. A photograph of the placenta is shown in Fig. 2.

Comment

This series of three cases of monoamniotic twins is unusual because all of the individuals survived. Difficulty with prolapsed knotted cords was encountered in only one case and this was treated by rapid delivery of the The only other complication, placenta previa, which is more common in twin pregnancies in general, was treated by cesarean section. In spite of the high incidence of fetal death reported in monoamniotic twin pregnancy, this misfortune was not encountered at the Jewish Hospital of Brookyln during the more than two-year period of observation.

Summary

- 1. The mechanisms of formation of identical twins including monoamniotic twins are briefly mentioned.
 - 2. The incidence of monoamniotic twin pregnancies is discussed.
- 3. Knotting of the umbilical cords, a complication of monoamniotic twin pregnancy, is described.
- 4. The cases of double survival of monoamniotic twins noted in the American literature are tabulated.
- 5. Three new cases of monoamniotic twin pregnancy with double fetal survival are described.

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PRIMARY PERITONEAL PREGNANCY*

A Case Report

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PRIMARY implantation of the trophoblast on a peritoneal surface is rare. As late as 1940, Novak¹ thought that this was not possible. Eastman² believed that the evidence in a case reported by Studdiford³ is excellent. Cases have been reported in recent years by Elzey,⁴ Baldwin,⁵ and Ahnquist and Lund.⁴

A case is here reported from the private service of Dr. Charles A. Gordon.

A primipara, aged 32 years, was admitted to St. Catherine's Hospital with severe abdominal pain. She felt like fainting and had fainted before leaving home. About five hours previously, while asleep, she had been seized with severe pain in the abdomen, for which she was given morphine. The pain was not relieved. There had been no vaginal bleeding since her last menstrual period, which had begun 32 days prior to admission, continuing for five days.

Her blood pressure was 110/75; pulse rate 90 per minute; the red blood count was 3.7 million per cubic milliliter; the white blood count was 16,800 per cubic milliliter; the hemoglobin was 10.4 Gm. per 100 c.c. and the hematocrit was 32 volumes per cent. The abdomen below the umbilicus was distended, generally tender, with great rebound pain. A fluid wave was readily demonstrated. On vaginal examination, a tender mass was felt in the posterior fornix, and motion of the cervix was very painful. The diagnosis was ruptured ectopic pregnancy.

At operation, under Pentothal sodium and cyclopropane anesthesia, about 500 c.c. of free and clotted blood was found in the peritoneal cavity. The uterus was soft and somewhat enlarged. The tubes and ovaries appeared to be normal. No blood exuded from either tube, and no clots were adherent to them. The ovaries exhibited intact, corrugated surfaces; no corpus luteum of pregnancy was seen, nor were any intestinal or omental adhesions present. There was no evidence of endometriosis in the pelvis.

An actively bleeding tumor was discovered on the mesentery of the ileum. It was ovoid, approximately 1.5 cm. in length and 0.5 cm. in width, dark red in color, and was situated about 3 cm. from the wall of the bowel, firmly adherent to the mesentery. Bright red oozing from the base of the tumor was vigorous.

The bleeding tumor was removed by sharp dissection and the surface defect was closed. The abdomen was closed in layers with interrupted cotton sutures. During the operation, 1,000 c.c. of blood was administered. The convalescence was uneventful.

The pathological report follows:

The specimen consisted of a rounded piece of tissue said to be from the mesentery, measuring 1.5 cm. in diameter. The external surface was reddish tan, slightly roughened and hemorrhagic. On cut section two cysts were noted, measuring 0.4 and 0.3 cm. in dimeter, respectively, filled with clotted blood. Microscopic examination showed that most of the tissue was composed of villi that had a delicate stroma with only an occasional formation of capillaries. The trophoblast cells were arranged in two and three layers.

^{*}Presented at a meeting of the Brooklyn Gynecological Society, May 16, 1956.

At one corner of some of the sections (Fig. 1) was seen a segment of fatty tissue from the mesentery. In the vicinity of this tissue there was noticed a fair amount of homogeneous, pink-staining material which showed focal infiltrations by polymorphonuclear leukocytes, lymphocytes, and plasma cells. The general appearance of this material was that of fibrin. Fragments of decidua-like tissue were noted in the vicinity of the villi.

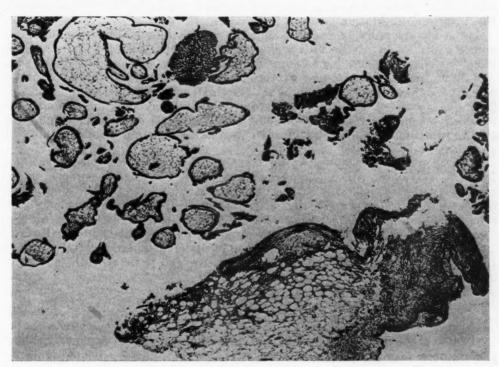


Fig. 1.—Demonstrates tissue from mesentery, young villi and fragments of decidua-like tissue. ($\times 32$; reduced $\frac{1}{16}$.)

Elzey⁴ stated, "It is comparatively easy to conceive of primary implantation if an abdominal pregnancy is an early one, if the adnexa are normal, and if the embedded ovum is several centimeters or more removed from the tubes and ovaries." While the implantation site in this case was not as high as the lesser peritoneal sac, as it was in the case reported by Elzey, it was some distance from the genital organs, and it is felt that this case fits his concept well. Other authors have stated criteria for proof of primary abdominal pregnancy more formally; Studdiford's³ criteria are:

"(1) That both tubes and ovaries are normal with no evidence of recent or remote injury, (2) the absence of any evidence of a uteroperitoneal fistula, and (3) the presence of a pregnancy related exclusively to the peritoneal surface and young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube."

The tubes and ovaries in this case were examined with care in an effort to find the bleeding point; both tubes were intact throughout their entire length, the lumina were patent and no blood or tissue could be expressed from their fimbriated ends. The ovaries also exhibited intact, corrugated surfaces.

Size, shape, and consistency of the uterus were compatible with the early period of gestation; the bladder was firmly adherent anteriorly and the posterior surface of the uterus was intact; the broad ligaments were intact. No uteroperitoneal fistula could be visualized.

Proof of an early pregnancy rests on two points. The first is that the patient had a normal period beginning 32 days prior to the acute episode of intra-abdominal hemorrhage. This period lasted 5 days and for the following 5 days coitus was performed without contraceptive devices, since that time was considered to be a "safe period." Subsequently contraceptives were used. The patient probably became pregnant within 5 days after her period, making the duration of gestation between 22 days and 27 days.

The second point of proof is that the microscopic sections demonstrated young villi. Most of the villi were without branching and without definite

blood vessels; in a few branching villi early vessels could definitely be seen.

According to Heuser and Streeter, and Hertig, the trophoblast of the macaque monkey shows villi on about the thirteenth day of development. By 15½ days some of the villi have a fairly distinct mesodermal stroma with vascular primordia, ranging from single stellate cells containing large vacuoles to solid multicellular strands. In the 22-day macaque ovum the villi are vascular.

The Ingalls embryo, of 35 days' menstrual age, is comparable to the ovum found in this case with a 32-day menstrual age. The Ingalls embryo, as described by Hertig, has villi with a variable vascular pattern. The simple villi possess a few isolated connected angioblastic strands that are usually solid or are beginning to show lumen formation. With increased branching of the villi the vascular pattern becomes more complex and is in the form of large irregular endothelial tubes having occasional small stubby branches. In all regions of the villus the vascular elements tend to lie beneath the epithelium.

While the ovum in this case cannot be dated with accuracy, the vilil are comparable to those described in the Ingalls embryo and they are in the stage of development that might be seen in an ovum 22 to 27 days of age.

To be other than a primary peritoneal implantation, this ovum would have had to abort into the peritoneal cavity almost immediately after implantation in the genital tract, be transported between the coils of ileum and reimplanted on the mesentery. Although transportation and reimplantation of a completely detached conceptus was once thought to occur, most recent authors4, 6, 9 do not believe this to be possible.

It is therefore concluded that the mesentery of the ileum was the primary site of implantation of this early ovum.

I wish to express my appreciation to Dr. Charles A. Gordon for permission to report this case and to Dr. Maximilian Wachstein for the description of the specimen.

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CENTRAL PLACENTA PREVIA DUE TO A SUCCENTURIATE LOBE

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(From St. Jerome Hospital)

THE usual significance of a succenturiate lobe arises through its possible undetected retention when it becomes a source of postpartum bleeding, uterine atony, and infection. Considering only those succenturiate lobes with a diameter of over 5 cm., Earn² noted an incidence of 0.25 per cent in 5,676 consecutive deliveries. That a succenturiate lobe might be implanted by chance in a central placenta previa location is understandably a most unlikely event. Except for a scattering of suggestive titles from the foreign literature, the Index Medicus lists only the reports of Deutschman,¹ Hess,³ and Siegler and Sachs.⁵ The following case report gives an example of such a medical oddity.

Case Report

E. S., a 32-year-old white married housewife, para ii, gravida iii, Rh positive, was first seen in consultation on admission to St. Jerome Hospital at 11:00 p.m. on June 3, 1955. The last menstrual period was on Sept. 23, 1954, and the estimated date of confinement, June 30, 1955. The serologic test for syphilis was negative. The pregnancy had been uneventful until one month previously when the onset of vaginal spotting was noted. At first, there was some fluid loss suggestive of leakage of amniotic fluid, but this did not persist. Seven hours prior to admission, the patient had the first of a series of three gushes of blood from the vagina. With great reluctance on her part, she was persuaded by her attending physician to enter the hospital.

On admission, her general condition was good and the bleeding amounted to only a slight staining of bright blood. The hematocrit was 37 and the hemoglobin 10.5 Gm. She was not in labor, although a few irregular Braxton Hicks contractions had been noted. None of the bleeding had been associated with pain. The fetus was floating in left occipitotransverse position and was estimated to weigh between 5 and 6 pounds. Blood was

obtained for cross-match and an expectant course was adopted.

Three hours after admission, a sudden gush of blood occurred, but there was no alteration in the vital signs. One and one-half hours after this, such a severe vaginal hemorrhage began that she was in deep shock with poor pulse, unobtainable blood pressure, cyanosis, and air hunger within ten minutes. Blood was given in both arms, and intensive shock therapy was carried out. The hemorrhage subsided during the depth of the shock and her condition was good within half an hour. When the shock was most marked, there was a brief period when the fetal heartbeat was slow and slightly irregular, but this did not persist.

With improvement in her general condition, delivery by a classical section was carried out under general anesthesia and a normal living 3,000 gram female infant was born. The placenta was implanted on the right lateral wall with its lower margin near the internal os. A marginal insertion of the cord was seen at its upper edge. Separate from the main body of the placenta was a 3 by 7 cm. succenturiate lobe which completely covered the internal os. This succenturiate lobe was only about two-thirds as thick as the main

placenta and was partially separated as a result of the beginning effacement of the cervix. The main body was still firmly attached. The relationships are illustrated in Fig. 1. With a temporary uterine atony and some increase in bleeding from the placental site, total blood loss during the operation was estimated at 1,000 c.c. Adequate blood replacement was given and the procedure was completed without further incident.

Of additional interest was the finding of a mild infectious hepatitis on the first postoperative day. Mild jaundice of three days' duration was accompanied by enlargement of the liver, 2 plus cephalin flocculation, prothrombin time prolonged to 24 seconds, and total proteins of 5.4 Gm. The patient then admitted to having had some diarrhea and fatty food intolerance for two weeks and confessed she had also been reluctant to report these symptoms to her attending physician.

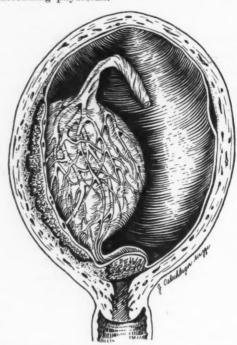


Fig. 1.—Succenturiate lobe covering the internal os.

The patient was discharged one week after delivery after an otherwise uneventful postoperative course. The clinical and laboratory signs of hepatitis had disappeared. Except for mild cervicitis, her follow-up has been negative over a nine months' period. The baby had a normal blood count at birth and at 3 days of age. She has been normal in development, growth, and behavior, and has shown no evidence of hepatitis.

Comment

Torpin and Hart⁶ found an 8 per cent incidence of bilobate placenta in 4,098 deliveries. They discussed examples where both lobes had a low implantation, surrounding but not necessarily covering the internal os. They pointed out how this could be confused with a true central placenta previa. As described by Deutschman and by Siegler and Sachs, only the fact that the blood supply of the offending succenturiate lobe did not arise directly from the cord separates their cases from the bilobate placentas, both cases having succenturiate lobes equal in size to the remainder of the placenta. The case reported by Hess is comparable to the case reported here in that two small succenturiate lobes combined to cover the internal os and produce a central placenta previa.

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Personal communications by Deutschman with Beck, DeLee, Williamson, and Caldwell disclosed no knowledge on their part of a similar occurrence. DeLee commented, however, that he had seen examples where "a tongue of tough fibrous tissue which has overlaid the os means a placenta succenturiata which has grown over the internal os." A better blood supply would permit survival of the succenturiate lobe to produce the results described by Hess and in this report.

It appears that this condition happens more often than is suggested by these few reports. Its importance lies in the listing of another condition to be considered in the differential diagnosis of the causes of bleeding in late pregnancy.

The complicating infectious hepatitis is considered a coincidence.4 Its only possible relationship is to the increased blood loss at delivery caused by the altered prothrombin time. The postpartum cervicitis is mentioned for completeness of reporting and is not considered significant.

I wish to thank Dr. William S. Andaloro for permission to report his case.

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FATAL POSTPARTUM CEREBRAL HEMORRHAGE

Report of a Case

JOHN C. BROUGHER, M.D., VANCOUVER, WASH.

(From the Vancouver Clinic)

TOXEMIA of pregnancy with its complications has always been a constant source of worry for the obstetrician. Until the present experience, I have felt that no fatal eclamptic complication would develop, if the mild and early symptoms of toxemia were treated and kept under control. Never before has a patient died of eclampsia in over 7,000 patients I have delivered.

Mrs. K., primigravida, aged 20 years, married 1½ years, first consulted me when approximately eight weeks pregnant. Her family history disclosed that she had an aunt who had died of toxemia and convulsions, which worried her a bit. Her weight was 121 pounds and she gave as her usual weight 125 pounds. Examination showed the following positive findings: Bilateral mastoidectomy scars, moderate dental repair, a colloid goiter, cold moist palms with bitten fingernails. The uterus was anteverted and enlarged to the size of a 7 to 8 weeks' pregnancy. The laboratory report was: hemoglobin 11.9 Gm. per 100 ml., red blood count 4.35 million, white blood count 9,000; Rh negative, blood Group IV-O. The urine was normal. The blood pressure was 138/80, and from three months' gestation to term, the blood pressure varied from 150/78 to 160/98 as the maximum. Three days before she entered the hospital in labor the blood pressure was 140/90. Her entire weight gain was 18 pounds. At eight months of pregnancy, two weeks before delivery, she had slight ankle edema. The urine was negative for albumin until three days before delivery, when the laboratory reported a trace.

She was a most cooperative patient during the entire pregnancy, had a good mental attitude, and her home life was excellent. She watched her diet and took the vitaminmineral supplement. After the edema appeared, she restricted the salt intake. She entered the hospital on Sept. 13, 1952, at 1:15 P.M. after labor had started at 11:00 A.M., about two weeks prematurely. Her temperature was 99.4° F., pulse 86, and respirations 20. The blood pressure was 140/90. The fetal heart tones were 152 per minute. She was given one 3 grain Tuinal capsule, 100 mg. of Demerol, and 1/200 grain of scopolamine. The cervix was completely dilated at 3:45 P.M. and spontaneous delivery of a healthy female infant occurred at 4:28 P.M. Intravenous Ergotrate was given and the placenta expelled. The patient lost a minimum of blood and was returned to her room in good condition. She was seen the next morning at 9:00 and nothing unusual in her condition was noted. She did not complain of headache when asked. Her blood pressure was 130/70. She had voided. At 1:00 P.M., she complained of gas and abdominal discomfort. I saw her at 5:00 P.M. because of upper abdominal pain. The nurse had started a return flow. The abdomen was flat and there was no evidence of tympanites. Her lips were slightly cyanotic, but the patient appeared cheerful, and had no impairment of breathing. Her blood pressure was 160/85, and there appeared to be a slight increase in the pitting edema of both ankles. At 8:00 P.M., the nurse reported that the patient was sleeping very soundly. She had not complained of headache, and her blood pressure was 140-80, temperature 100, pulse 56, respirations 16. There was a little cyanosis, and her only complaint was abdominal. At 10:45 P.M., her face was swollen and she was perspiring. The blood pressure was 140/90. At 11:00 P.M., she showed increased cyanosis, and respiration became labored. The pulse was 64 and blood pressure 150/92. She rapidly became comatose and failed to respond. Blood-tinged mucus began to appear in her nose and throat. The blood pressure was now 169/98. Oxygen was given, and in thirty seconds respirations ceased. Her color became deeply cyanotic and there was a feeble rapid pulse for three hours while she was given positive pressure oxygen by the hospital anesthetist.

A summary of the pathological findings reported by Dr. Robert Johnston is as follows:

The immediate cause of death of this young mother may be attributed to a massive spontaneous intracerebral hemorrhage of the left cerebral hemisphere complicated by the development of pulmonary hyperemia and edema and early terminal bronchopneumonia. The primary cause of death should be coded as eclampsia, however, morphologically substantiated by hemorrhagic intralobular periportal necrosis of the liver and parenchymatous degeneration of the kidneys.

Brain Addendum.—Following fixation in formalin, the brain was carefully sectioned coronally at intervals of 1.0 cm. The hemorrhage within the left cerebral hemisphere had destroyed the white matter of the corona radiata and extended from and involved the frontal, parietal, and even a portion of the occipital lobe. Numerous punctate hemorrhages within the white matter surrounded the area of massive hemorrhage. The corpus striatum was destroyed and the hemorrhage had ruptured into the left lateral ventricle. The septum pellucidum was likewise ruptured and the right ventricle also contained blood. The only other finding of note within the brain was a single area of focal hemorrhage within the pons; this area measured approximately 0.4 cm, in diameter.

Comment

This case illustrates essentially postpartum eclampsia with few antecedent warnings of impending toxemia.

Tatum¹ found no antecedent toxemia in 36 cases of postpartum eclampsia. Stander² reported 24 cases of eclampsia post partum with 54 per cent

Way³ reported two instances of massive cerebral hemorrhage in 33 patients who died of eclampsia.

showing no antepartum toxemia.

Dieckmann,⁴ reviewing fatal cases of eclampsia, reported extensive cerebral hemorrhage in 15 to 20 per cent of the autopsies.

The blood pressure recordings were never high enough to cause suspicion that a fatal cerebral accident might terminate this life. If the Ergotrate given immediately postpartum caused a sudden rise in the blood pressure, it was not recorded by the anesthetist.

The absence of headache at any time in this patient gave us little indication of what was happening. The abdominal discomfort 24 hours after delivery was the only clue to eclampsia, and this was not recognized as a symptom of impending danger. The mildly toxemic patient usually recovers quite promptly after delivery. This patient had sufficient spasm and thrombosis of hepatic and cerebral vessels that hemorrhage and death resulted instead of recovery.

Summary

This case report illustrates how cerebral hemorrhage may complicate and cause fatal termination of pregnancy where there have been few symptoms of

The arteriolar spasm with thrombosis in cerebral, hepatic, and renal blood vessels produced ischemic necrosis and hemorrhage in the brain, liver, and kidneys.

The postpartum abdominal discomfort was not recognized as a symptom of toxemia. The absence of headache or increased hypertension masked the clinical picture. There was no evidence of a convulsive seizure, although the respirations were significantly increased as seen in impending toxemia. The onset of coma without convulsions is quite unusual.

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 Dieckmann, W. J.: The Toxemias of Pregnancy, ed. 2, St. Louis, 1952, The C. V. Mosby Company.



Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

The Care of the Expectant Mother. By J. Barnes. 270 pages. New York, 1956, Philosophical Library. \$7.50.

This volume was written as a "practical guide for all who undertake the management of pregnancy." It is divided into three sections, the first of which deals with normal pregnancy. One chapter in this section describes the maternity services available in Great Britain under the National Health Act. It is interesting to note that a general practitioner, if qualified to do obstetrics (i.e., if he has his name on the "obstetric list"), must render complete obstetric care including care of the newborn for the sum of 5 pounds 5 shillings (about \$14.70). There are many other similar details in this chapter which are somewhat alarming to physicians who practice in countries where medicine is not controlled by the state.

Section II deals with abnormalities of pregnancy and Section III with diseases complicating pregnancy. In general, most details of diagnosis, management, and treatment correspond with those ordinarily used in the United States, with some minor exceptions.

This volume seems intended for midwives and nonspecialists and contains considerable basic information which is presented in an oversimplified fashion. The book should be of practical use to someone who does occasional obstetrics.

Expectant Motherhood. By N. J. Eastman. Third edition, 198 pages. Boston, 1957, Little, Brown, & Company. \$1.75.

The prospective mother will find this a particularly valuable book because it clearly and concisely explains all aspects of pregnancy. It is easily understood by the lay reader and, because it anticipates her problems, the book helps her to assuage fears and gain confidence.

The third edition is especially complete with chapters on all phases of pregnancy and birth, including signs of pregnancy, growth and development of the fetus, diet and hygiene in pregnancy, common discomforts, danger signals, and birth of the baby. Many concepts, accepted for years, have been revised or supplemented according to recent advances in obstetrics.

The book's small size makes it convenient for carrying in a handbag where it is available for easy reference and reassurance.

Principles of Urology. By M. F. Campbell. 622 pages, 319 illustrations. Philadelphia, 1957, W. B. Saunders Company.

This basic test is designed principally for the medical student but is also useful as a reference for the practitioner desiring a condensed review of a urological topic. The author, having written *Pediatric Urology* and edited a three-volume encyclopedic text, is particularly qualified to present this textbook. The book discusses the subject matter of urology under topics such as tumors, injuries, obstructions, etc. This method has advantages, but also the disadvantage of forcing the student to look back to general discussions of urologic anatomy and physiology rather than having unified all material dealing with an organ.

Two innovations that should prove helpful in orienting students are the section on semantics and word usage of urology and the series of comprehensive questions encompassing the entire pertinent subject matter of urology. The illustrative matter is drawn mainly from the author's previous work and is of excellent quality. The common problems of gynecology and urology are ably and completely presented in chapters on the adrenal glands and on urology in the female.

A minor criticism of this textbook is that in some instances the only treatments discussed are those advocated by the author; other equally accepted methods are not.

Modern Office Gynecology. By G. Blinick and S. A. Kaufman. 218 pages, 47 figures. Philadelphia, 1957, Lea & Febiger. \$4.50.

This useful volume is divided into three sections. There are descriptions of common gynecological conditions in the first, 47 figures of various techniques, office procedures, and microscopic scenes in the second, and an annotated bibliography with clinical abstracts in the last.

The smallness and compactness of size are an advantage for quick reference, but of course such a condensed version cannot be as meaningful as a more complete text.

The Use of Muscle Relaxant Drugs in Anesthesiology. By F. Foldes. 210 pages. Springfield, Ill., 1957, Charles C Thomas, Publisher. \$5.50.

It has been expected that a book on muscle relaxants in anesthesiology would appear. Since the introduction of curare by Griffith and Johnson in 1942, these drugs have revolutionized anesthetic practice. As always, new agents bring with them a host of problems and complications. Therefore, this short monograph is not only timely, but also stimulating in its precision of detailing them.

The book is divided into two complementary sections. The first is "Basic Considerations." The attractive format, tables, and illustrations depict the action of these drugs in clear, concise fashion. The differentiation of the action of these drugs as depolarizing and nondepolarizing agents makes for a working hypothesis which is both understandable and simple. The argument is skillfully presented and admirably documented by an extensive bibliography whose utility will be appreciated by the expert.

The second section, "Clinical Use," to which two-thirds of the monograph is devoted, presents in precise detail both the techniques and philosophy of Dr. Foldes in regard to the use of muscle relaxants in anesthesiology. This presentation, while useful, presents opinion as well as the clinical practice of the author. While a laudable effort has been made to place dosage on a quantitative basis, in actual practice, dosage schedules may be subject to considerable variation. To be most useful, the text should be taken as a guide for the reader rather than a catechism. Attention should be called to the excellent discussion of apnea following use of muscle-relaxant drugs.

BOOKS RECEIVED

The following books have been received. Selected reviews will appear in later issues.

- Liver, Biliary Tract and Pancreas. By F. H. Netter. Part III of Volume 3, The Ciba Collection of Medical Illustrations. 165 pages, 133 plates. New York, 1957, Ciba Pharmaceutical Products, Inc. \$10.50.
- Martius' Gynecological Operations. Translated and edited by M. L. McCall and K. Bolton. 397 pages, 450 illustrations. Boston, 1957, Little, Brown, & Company. \$20.00.
- 1957 Medical Progress. Edited by M. Fishbein. 367 pages. New York, 1957, Blakiston Company (division of McGraw-Hill Book Company, Inc.). \$6.00.
- The Metabolic Response to Neonatal Surgery. By P. P. Rickham. 93 pages. Cambridge, Mass., 1957, Harvard University Press.
- Perinatal Loss in Modern Obstetrics. By R. E. L. Nesbitt, Jr. 432 pages, 108 illustrations. Philadelphia, 1957, F. A. Davis Company. \$12.50.
- Pioneer Surgeons of the Woman's Hospital. By J. P. Marr. 148 pages. Philadelphia, 1957, F. A. Davis Company. \$5.50.
- Principles of Surgical Physiology. By H. A. Davis. 841 pages. New York, 1957, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers). \$20.00.
- Surgical Gynecology. By J. P. Greenhill. Second edition, 377 pages, 107 illustrations. Chicago, 1957, The Year Book Publishers, Inc. \$9.50.
- Urologic Injuries in Gynecology. By H. C. Falk. 265 pages, 97 figures. Philadelphia, 1957, F. A. Davis Company. \$7.50.
- Women Doctors of the World. By E. P. Lovejoy. 413 pages, 49 illustrations. New York, 1957, The Macmillan Company. \$5.95.

SELECTED ABSTRACTS*

The American Journal of Pathology

Volume 33, March-April, 1957.

*Ober, W. B., Grady, H. G., and Schoenbucher, A. K.: Ectopic Ovarian Decidua Without Pregnancy, p. 199.

Ober, Grady, and Schoenbucher: Ectopic Ovarian Decidua Without Pregnancy, p. 199.

This article reports 16 instances of ectopic ovarian decidua in patients who were not pregnant. The authors outline the historical background for this entity as well as the possible embryologic explanation. Most of the areas of ectopic decidua were in close proximity to a corpus luteum and many were associated with some inflammation.

The decidual response results because of stimulation of the subcelomic cells by radition or inflammation in the presence of progesterone. The progesterone comes from the stimulated corpus luteum or possibly the adrenal cortex.

J. EDWARD HALL

^{*}Titles preceded by an asterisk are abstracted below.

Archivos cubanos de cancerología

Volume 16, January-March, 1957.

*Vera, G. H.: Sarcoma Botryoides of the Bladder in a Child, p. 59.

Vera: Sarcoma Botryoides of the Bladder in a Child, p. 59.

The author reports a case of sarcoma botryoides of the urinary bladder in a white male child. Symptoms of dysuria and difficult micturition with an abdominal mass appeared at 2 months of age. This was followed by infection. The child was seen when 4 months of age at which time a diagnosis of sarcoma botryoides was made. Deep x-ray therapy (700 r) was given. Because of the wide extent of the tumor, surgical resection was limited to local excision. The child died two months later.

Although this condition is rare, early symptoms can be confused with those of congenital stricture of the urethra. Three-year survivals have been reported with complete cystectomy.

FRANCIS B. O'BRIEN

The Canadian Medical Association Journal

Volume 76, April 15, 1957.

Quinlivan, W. L. G.: Compound Presentation, p. 633.

The Journal of the American Medical Association

Vol. 160, March 17, 1956.

*Krainin, P., and Lapan, B.: Neonatal Hepatitis in Siblings, p. 937.

Krainin and Lapan: Neonatal Hepatitis in Siblings, p. 937.

Two infants, one male and the other female, died shortly after birth. Postmortem findings were similar to those in some forms of erythroblastosis. Liver biopsy and function tests showed that the mother's liver was similarly involved. Unusual sensitivity of the mother to diethylstilbestrol and viral infection were considered etiological factors. The resemblance of these cases to erythroblastosis, however, suggested the possibility of incompatible blood factors of some rare or unknown type.

DAVID P. BAUER

Vol. 160, March 24, 1956.

*McNally, H. B., and Fitzpatrick, V. de P.: Patients With Four or More Cesarean Sections, p. 1005.

*Norment, W. B., and Sikes, C. H.: Photographing Tumors of the Uterine Canal in Patients, p. 1014.

McNally and Fitzpatrick: Patients With Four or More Cesarean Sections, p. 1005.

The obstetric histories of 130 patients with four or more cesarean sections are reviewed. Low cervical cesarean section was the operation most often done, and it was found that this operation contributed less to rupture of the uterus than the classical type of operation. The data also show some increase in prematurity which is interpreted as anxiety on the part of the operator to avoid the risk of rupture. No conclusion is drawn concerning the relative safety of vaginal deliveries after cesarean section, but it is felt that the capabilities of the uterus after multiple sections have been underestimated.

DAVID P. BAUER

Norment, and Sikes: Photographing Tumors of the Uterine Canal, p. 1014.

A method of inspecting the cervical canal and the uterine cavity is described. The water hysteroscope is used. Photographs are made by attaching an endoscopic camera. Water is allowed to flow into the hysteroscope on the right side, through the lumen of the uterus, and out the left side. It is possible to visualize both cornua up to the openings of the oviducts. The technique has been used for seven years without complications.

DAVID P. BAUER

Volume 161, June 16, 1956.

Goldfarb, A. F., and Napp, E. E.: Use of Methallenestril (Vallestril) in Control of Menopausal Symptoms, p. 616.

Volume 161, June 30, 1956.

Guttmacher, A. F.: Factors Affecting Normal Expectancy of Conception, p. 855.

The Journal of Clinical Endocrinology and Metabolism

Volume 17, April, 1957.

*Venning, E. H., Primrose, T., Caligaris, L. C. S., and Dyrenfurth, I.: Aldosterone Excretion in Pregnancy, p. 473.

Venning, Primrose, Caligaris, and Dyrenfurth: Aldosterone Excretion in Pregnancy, p. 473.

The authors measured the aldosterone excretion at monthly intervals in the prenatal period and immediately post partum in 4 women with normal pregnancy and at near term in 8 women with toxemia of pregnancy. The aldosterone excretion gradually increased during pregnancy but returned to normal rapidly after delivery.

The rapid accumulation of fluid in 2 patients was associated with a rising level of aldosterone output. However, the levels reached were no higher than those observed in pregnant women without clinical edema.

The amount of aldosterone excreted was not greater in patients with toxemia than in the normal gravid patients.

The reason for the increase in aldosterone excretion during pregnancy is not known. Neither is it known whether or not the increase in aldosterone is the cause of the accumulated fluid in some patients.

J. EDWARD HALL

The Lancet

Vol. 2, October 13, 1956.

*Holmes, J. M.: Amiphenazole in Obstetric Analgesia, p. 765.

Holmes: Amiphenazole in Obstetric Analgesia, p. 765.

The author reports on the clinical trial of a morphine antagonist, Amiphenazole (2:4-diamino-5-phenylthiazole hydrochloride). This drug is described as being relatively harmless, healthy volunteers having received up to 300 mg. intravenously without adverse effects. In the dosage recommended, Amiphenazole was shown to reduce neonatal apnea caused by morphine, but was not capable of eliminating this entirely.

DOUGLAS M. HAYNES

Vol. 2, December 29, 1956.

*Carter, R. E. B., Bound, J. P., and Smellie, J. M.: Mean Venous Pressures in the First Hours of Life, p. 1320.

Carter, Bound, and Smellie: Mean Venous Pressures in the First Hours of Life, p. 1320.

By means of an ingenious apparatus, the mean venous pressure was measured through the umbilical vein in 5 groups of babies: (1) 35 normal babies, (2) 12 babies who had required resuscitation at birth, (3) 32 babies with respiratory difficulty, (4) 8 babies with cerebral irritation, and (5) 5 babies with erythroblastosis fetalis.

In the healthy babies, the mean venous pressure (supine) was 2.6 cm. of 5 per cent dextrose solution (S.D. \pm 1.2 cm.). Neither the birth weight nor the age during the first 18 hours of life affected the mean venous pressure. When these babies were tipped feet downward, the mean venous pressure became -2.0 cm. (S.D. \pm 1.5). Only one baby in Group 2 had a venous pressure higher than normal. In Group 3, the venous pressure was measured during the first 6 hours in 25 babies and found to be 5.7 cm. (S.D. \pm 2.7) which was significantly higher than normal. Eight of these babies died and in these the venous pressure was normal as contrasted with a high venous pressure in 10 of the 17 survivors.

The suggestion is made that the high venous pressure may be beneficial in increasing cardiac output which may assist in expanding the lungs.

In the 7 babies in whom the venous pressure was measured after 6 hours of life, a normal pressure was found in all but 2 and all of these babies survived. Serial determinations were made in 5 infants in this group. In each case the venous pressure fell and in the 3 survivors the pressure became normal with clinical improvement. In Group 4, the venous pressure was 5.0 cm. or more in 3 babies and normal in 5. All survived. In Group 5, the 4 survivors had increased venous pressure prior to exchange transfusion. The fifth baby had a normal venous pressure and a hyaline membrane was discovered at necropsy.

Of the 8 patients in Group 3 who died, all were premature, 4 had hyaline membranes, 2 had resorption atelectasis, one a pulmonary hemorrhage, and one was not autopsied.

In 6 babies with increased venous pressure, tipping caused a mean fall of 6.5 cm. (normal 4.9 cm.) and in 14 abnormal babies with normal venous pressure, tipping caused a fall in venous pressure similar to that which occurs in normal infants.

In view of the possibility of beneficial results of a high venous pressure, the suggestion is made that the position in which an infant with respiratory difficulty is usually nursed may be harmful in that the venous pressure is decreased when the infant is tipped feet downward.

DAVID M. KYDD

Volume 1, January 19, 1957.

*Roberts, H., Kane, K. M., Percival, N., Show, P., and Please, N. W.: Effects of Some Analgesic Drugs Used in Childbirth, p. 111.

Roberts, Kane, Pervical, Show, and Please: Effects of Some Analgesic Drugs Used in Childbirth, p. 111.

This is a study of the alteration in respiratory minute volume in the newborn infant following administration of various analgesic agents to the mother in labor at the Hammersmith Hospital, London.

The mean minute volume of 565 newborn infants whose mothers had received gas and air was compared with that of 205 newborns whose mothers had received Pethidine in addition to gas and air. The authors found that the minute volume in the Pethidine group was reduced by 10 to 15 per cent. Furthermore, the authors evaluated the effectiveness of levallorphan as an antagonist to Pethidine. The measured mean minute volume of 177 newborn babies whose mothers had received Pethidine, gas, and air was compared to the mean minute volume of 178 infants whose mothers had received levallorphan in addition to Pethidine, gas, and air. They found no significant increase in the mean minute volume in the latter group.

In this study, the minute volumes of the newborn infants were recorded with a trip spirometer described originally by Donald and Lord in 1953.

VINCENT TRICOMI

Volume 1, February 2, 1957.

Mann, T. P., and Elliott, R. I. K.: Neonatal Cold Injury Due to Accidental Exposure to Cold, p. 229.

Volume 1, February 9, 1957.

Huges, R. T.: Acute Porphyria in Pregnancy, p. 301.

Volume 1, February 16, 1957.

*Walker, W., Murray, S., and Russell, J. K.: Induction of Labor to Prevent Recurrent Stillbirth Due to Hemolytic Disease, p. 348.

*Young, S., Bulbrook, R. D., and Greenwood, F. C.: The Correlation Between Urinary Estrogen and Vaginal Cytology, p. 350.

*Oppe, T. E., Hsia, D. Y., and Gellis, S. S.: Pregnancy in the Diabetic Mother With Nephritis, p. 353.

Walker, Murray, and Russell: Induction of Labor to Prevent Recurrent Stillbirth Due to Hemolytic Disease, p. 348.

During a three-year period, 108 women seen early in pregnancy had previously had a stillbirth attributable to hemolytic disease. Sixty of these pregnancies were selected for induction of labor 35 days before the expected date of delivery. Thirty-seven still-births and 23 instances of severe hemolytic disease resulted. However, 28 of these still-births occurred prior to the intended date of induction.

The pregnancy was allowed to end spontaneously: (a) In 6 cases because the women were first seen in labor at term. All of these were Rh positive. There were 5 stillbirths and the live baby had severe hemolytic disease. (b) In 27 cases because the father was heterozygous D/d. Thirteen of these mothers were Rh positive; they had 9 stillborn infants and 4 with severe hemolytic disease. (c) In 15 cases because the previous stillbirth was considered very doubtfully due to hemolytic disease. Among these there were 14 Rh positive mothers who had 3 stillbirths, only 1 of which was caused by classical hydrops fetalis. In the liveborn infants, the severity of the illness was similar to that reported in unselected material (7 severe and 4 mild instances of hemolytic disease).

Considering only the pregnancies which lasted 35 weeks, induced termination resulted in 23 live births and 9 stillbirths, whereas spontaneous termination resulted in 5 live births and 10 stillbirths. Apparently these latter figures were obtained by not considering the patients in (c) and the instances of negative Rh in (a) and (b). The difference between the results in the induced-labor and spontaneous-labor groups was considered to be significantly in favor of premature induction (P = 0.02 - 0.01) in spite of including 7 infants in the induced group and 3 in the spontaneous group who although undelivered were already dead or hydropic at 35 weeks. If these were eliminated, the difference was believed to be highly significant (P = 0.004).

The liveborn babies had severe hemolytic disease. The average cord blood hemoglobin concentration was 10 Gm. per cent and nearly 50 per cent of the infants had cord bilirubin concentrations higher than 5 mg. per cent. All were treated by exchange transfusion although in anemic babies this was accomplished by repeatedly transfusing smaller amounts. The exchange transfusion was repeated in instances in which a bilirubin level of 25 mg. per cent was found during the first 6 days of life. Nine of the 18 survivors in the induced group required multiple exchange transfusions. None of the 5 survivors in the spontaneous group became so deeply jaundiced as to require repeated exchange transfusions. Four of the 5 babies who died following the induced delivery died during the course of exchange transfusion. No explanation for this ordinarily rather rare event was found although on necropsy 2 infants had severe pneumonia and 3 had pronounced cardiomegaly. In addition, tentorial tears, hyaline membranes, and pulmonary hypoplasia were present in some cases.

The comment was made that many stillbirths from hemolytic disease occur early in pregnancy but, if there has been a previous stillbirth from hemolytic disease and if the fetus reaches the age of 35 weeks' gestation and is not hydropic on x-ray examination, premature induction results in a greater percentage of live babies (perhaps 80 per cent) than spontaneous delivery. However, the premature baby with severe hemolytic disease presents a most difficult therapeutic problem.

DAVID M. KYDD

Young, Bulbrook, and Greenwood: The Correlation Between Urinary Estrogen and Vaginal Cytology, p. 350.

The correlation between vaginal cytology and amount of estrone, estradiol- 17β , and estriol in the urine as determined by the method of Brown (Biochem. J. 60: 185, 1955) was studied on 75 occasions in 53 pre- and postmenopausal women whose ages ranged from 26 to 80 years.

The vaginal fluid was cytologically graded (1) into 1 of 5 grades by simple inspection, (2) into 1 of 4 grades from glycogen index, (3) by differential cell count and calculation of deep index, (4) by differential cell count and calculation of the pyknotic index, (5) by differential cell count and calculation of the cornified index, and (6) into 1 of 5 grades from the differential count.

After statistical analysis, the conclusions were: (a) the urinary output of estriol correlates with all the grading methods used to assess estrogenic stimulation of the vagina, (b) the total output of estrogen correlates with all methods except the glycogen index, (c) the output of estrone correlates with grading by simple inspection and by differential cell count, (d) the output of estradiol correlates with none of the cytological methods, and (e) the comparison between the output of estriol and the grading of vaginal cytology by simple inspection gave the best correlation. The following arithmetic means of estriol values were found in each estrogen grade that had been made by simple inspection: 1.4 meg. (S.D. 2.049) in grade 0, 2.8 meg. (S.D. 3.268) in grade 1, 4.05 meg. (S.D. 4.468) in grade 2, 10.38 meg. (S.D. 9.116) in grade 3.

The value of the correlation appeared to be statistical rather than practical in view of the wide standard deviation and considerable overlap in output of estrogen from one group to another. Serial cytologic studies made in the same individual, however, were found to provide a good estimate of the changing urinary estrogen excretion from time to time. Conversely, the urinary output of estrogen provided an accurate reflection of estrogen effect on the patient.

DAVID M. KYDD

Oppe, Hsia, and Gellis: Pregnancy in the Diabetic Mother With Nephritis, p. 353.

Of 767 pregnancies complicated by long-standing diabetes and lasting at least 28 weeks, 31 occurred in women who, when the pregnancy became known, had chronic renal disease with nitrogen retention. Ten other pregnancies similarly complicated were terminated naturally or artificially prior to 28 weeks. Other complications such as retinitis proliferans, etc., were not considered in this study and the precise nature of the renal disorder, whether chronic capillary glomerulosclerosis, pyelonephritis, or both, remained uncertain. Of these 41 mothers, 15 were primigravidas, 19 had had 1 previous pregnancy, and 7 more than 1. Although there was no maternal death, 2 of these pregnancies ended in miscarriage and 8 in therapeutic abortion because of advancing renal disease or retinitis. Four stillbirths occurred and there were 8 neonatal deaths. Nineteen children survived (61 per cent of the viable fetuses). These results were compared with the experience in 736 viable pregnancies in women with diabetes but without renal disease who attended the same clinic. Among these latter, there were 53 stillbirths, 84 neonatal deaths, and 599 survivors (82 per cent).

In the present series, the 4 intrauterine deaths occurred at 29, 31, 32, and 33 weeks, which is earlier than is usual in uncomplicated diabetes. However, the pregnancy was

ended as soon as evidence of fetal distress appeared, so that additional later intrauterine deaths may have been forestalled. All but 6 of the pregnancies were ended by cesarean section. Of 27 liveborn babies, 17 developed respiratory distress. Eight died; 6 of these had the hyaline membrane and resorption at electasis so frequently associated with maternal diabetes. The birth weights of babies of diabetic mothers born before the thirty-third week of gestation were about the same whether or not the mother had renal disease. However, babies whose mothers had renal disease were distinctly smaller when comparison was made between the thirty-third and thirty-seventh weeks of pregnancy. The small size of these infants together with the tendency to early intrauterine death was believed to indicate an unfavorable environment for the fetus.

All told, with expert diabetic and obstetric management, only 45 per cent of these pregnancis resulted in a surviving child. The comment is made that such a risk must be added to the danger of such pregnancies to the health of the already ill mother.

DAVID M. KYDD

Volume 1, March 16, 1957.

*Boyes, J., Bremner, A. E., and Neligan, G. A.: Hematogenous Osteitis in the Newborn, p. 544.

Boyes, Bremner, and Neligan: Hematogenous Osteitis in the Newborn, p. 544.

Of 40 cases of neonatal osteitis, 21 were considered severe and 19 mild. From 24 of these patients a Staphylococcus was recovered that was resistant to penicillin in vitro in 16 instances, sensitive in 7, and not tested in 1. Streptococcus hemolyticus was isolated from 5 patients, a Pneumococcus from 2, and Escherichia coli from 1. All of these latter organisms were sensitive to either penicillin or streptomycin.

Though the mildest infections tend to heal spontaneously, the severe are characterized by rapid dissemination and formation of metastatic abscesses in bone or vital organs. A seemingly mild infection may very suddenly become severe or develop recurrences. Therefore, as soon as the diagnosis is suggested by swelling, with or without discoloration of the skin, excessive irritability, relative immobility of a limb, signs of general infection with or without fever, or by a combination of these signs, therapy should be instituted.

Until the sensitivity of the infecting organism was determined, penicillin and chlortetracycline were administered. Of the 40 patients, one died and one was not followed adequately. Thirty-one of the remaining patients were treated for an average of 34 days (19 to 116 days). Although 25 patients (12 severe cases and 13 mild) recovered completely, 6 had one or more recurrences. Of 7 patients whose therapy averaged but 7 days (4 to 13 days), 6 patients had 12 recurrences between them.

In instances of swelling over the lesion, aspiration of pus was attempted and as much as 320 ml. was obtained from one 8 pound baby. No immobilization was used until after the infection had subsided.

Therapeutic failures were ascribed to inadequate surgical drainage of abscesses, insufficient treatment with antibiotics, and late diagnosis. Early diagnosis was stressed. Of 5 patients in whom the upper end of the femur was involved, in 4 the institution of therapy was delayed for 5, 8, 20, and 27 days. All of these 4 patients were left with permanently damaged hips.

The disease is a most serious one in that one infant died and more than one fourth of the children had as a residual either a destroyed or grossly distorted joint.

DAVID M. KYDD

Volume 1, March 23, 1957.

*Brun, C., and Munck, O.: Lesions of the Kidney in Acute Renal Failure Following Shock, p. 603.

*Higgins, L. G.: Rupture of the Pregnant Uterus, p. 618.

Brun, C., and Munck, O.: Lesions of the Kidney in Acute Renal Failure Following Shock, p. 603.

Of 33 patients who developed acute renal failure following shock caused by a variety of conditions, 24 died and 9 survived. Twenty biopsies were done on 17 patients between the second and sixty-sixth days after development of anuria. In 16 remaining patients, kidneys were studied at autopsy and, in 3 patients, both biopsy and necropsy specimens were studied. In the instances in which repeat studies were done, histological changes occurred with nearly the same frequency in both early and later stages of the disease. In only one did there seem to be an extension of the process.

The characteristic alterations were dilatation and flattening of the epithelium in the distal convoluted tubules, the presence of pigmented casts in the lower nephron, and hydropic transformation of the protoplasm of the epithelium of the proximal tubules. Necrosis of the tubular epithelium was uncommon. The contrast between moderate structural changes that were observed and complete functional breakdown was emphasized. Seven photomicrographs are included.

DAVID M. KYDD

Higgins: Rupture of the Pregnant Uterus, p. 618.

In the course of 20 years during which 23,000 deliveries were performed at the Working Maternity Hospital, rupture of the pregnant uterus was observed on only 3 occasions.

In one instance the rupture occurred suddenly at term in a woman who had had 2 previous normal pregnancies. The other 2 ruptures occurred prior to term (at 35 weeks and 4 days before term) both during sleep; in each of these 2 cases, curettage had been done prior to the pregnancy. The possible relationship between curettage and pregnancy is emphasized.

DAVID M. KYDD

Wiener medizinische Wochenschrift

Vol. 107, January 19, 1957.

*Picha, E., Rockenschaub, A., and Weghaupt, K.: Contribution to Management of Hemostasis in Operative and Conservative Gynecology, p. 74.

Picha, Rockenschaub, and Weghaupt: Contribution to Management of Hemostasis in Operative and Conservative Gynecology, p. 74.

The authors describe their experience with Reptilase, an extract of Brazilian snake venom obtained from Bothrops jararaca. This derivative of snake venom contains a blood-clotting enzyme, the hemocoagulase of Klobusitzky, which, when injected either parenterally or subcutaneously, promotes clotting throughout the body without a concomitant tendency to clinically significant thrombosis or embolism. The authors found that in patients with acute hemorrhage following irradiation therapy and vaginal plastic operations, the bleeding time was lowered to one fourth its normal value and the clotting time to one third its normal value within 25 minutes of the injection, and the starting values were not again reached for 60 to 65 hours. There was no change in platelets or prothrombin.

The authors treated 8 patients who had hematuria following irradiation treatment of gynecologic cancer; some of these patients had radiation cystitis with hematuria, and others had late rupture of damaged blood vessels. Forty-seven patients with rectal bleeding following irradiation treatment were also treated. Twenty patients who were scheduled for vaginal plastic operations were given Reptilase preoperatively to decrease operative bleeding and improve the visibility of the surgical field. The authors found this preparation to be especially helpful in reducing operating time in older women with genital prolapse. The results in metrorrhagia and menorrhagia were uniformly poor, and therefore this preparation cannot be recommended in such diseases.

DOUGLAS M. HAYNES



Correspondence

Prognosis of Tuboplasty

To the Editors:

I wish to congratulate Mr. Ostry for his frank, revealing, and courageous report on selection of patients for tuboplasty (Am. J. Obst. & Gynec., February, 1957, p. 409). For some years I have been vexed by the reports from my friends and colleagues concerning their glamorous results. I found it difficult to believe that diseased, blocked Fallopian tubes could be so successfully repaired and complete function restored by tuboplastic methods. The specter of extrauterine pregnancy and spontaneous abortion dimmed my vision of the anticipated birth of a viable fetus.

In cases where I have diagnosed obstructed Fallopian tubes, I have usually given a prognosis of a possible 2 per cent success in cornual implantation and 10 to 15 per cent in ampullar or fimbrial plastic. I now find myself embarrassed by my liberal prognosis and feel that I should retreat further to conservatism.

Since 1924, I have repeatedly warned in my publications that tubal tests bear the most careful interpretation. This is especially true in the diagnosis of isthmic and cornual closure. Most physicians using contrast media for diagnosis of tubal patency or closure have experienced one or more times what Mr. Ostry reported—normal pregnancy spontaneously and promptly following a negative Rubin test with gas or oil.

Such occurrences in the mid-twenties sent me back to the laboratory for study and re-evaluation of my results. I found that even 3 tests, with or without drugs (antispasmodic, narcotic, sedative), whether gas or liquid contrast medium be used, are not at times sufficient to diagnose tubal occlusion or closure correctly.

This short but forceful report by Ostry should be read by all interested gynecologists and surgeons. Some faces will be red!

IRVING F. STEIN, SR., M.D.

30 North Michigan Avenue Chicago 2, Illinois Feb. 12, 1957



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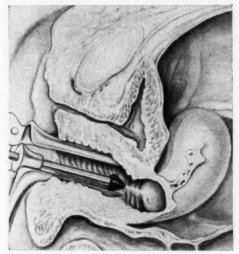
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Candidates for admission to the Examinations are required to submit with their application an unbound 8½ by 11 inch typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application. This information is to be attested to by the Record Librarian, Superintendent, or Director of the hospitals where the patients are admitted.

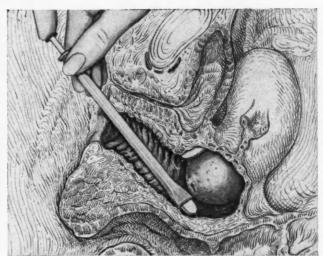
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Marriott, H. J. L.: Medical Milestones, Baltimore, Williams & Wilkins Company, 1952, pp. 269-270.

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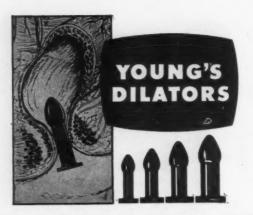
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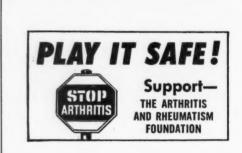
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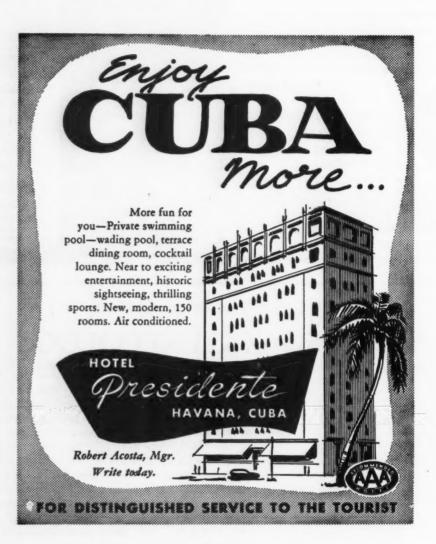
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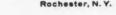
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